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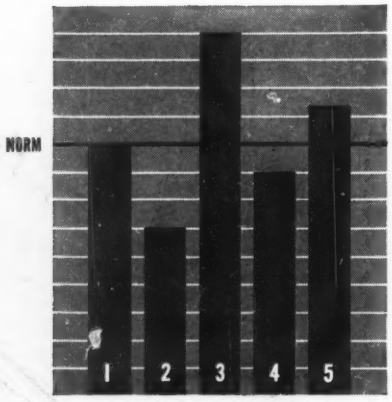


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# STUDIES IN GROWTH

## I. INTERRELATIONSHIP BETWEEN PITUITARY GROWTH FACTOR AND GROWTH-PROMOTING ANDROGENS IN ACROMEGALY AND GIGANTISM.* II. QUANTITATIVE EVALUATION OF BONE AND SOFT TISSUE GROWTH IN ACROMEGALY AND GIGANTISM**

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IN 1941, Albright while searching for serum phosphatase elevation in acromegalics (which incidentally he failed to find) noted significant elevation of the serum inorganic phosphorus in these patients. In going over the records of the same group of acromegalics, one of us became aware of certain significant findings and evolved therefrom a dual hypothesis.

The findings were: *First*, that as above noted, almost all untreated acromegalics had abnormally high serum inorganic phosphorus values; the only exceptions were a few female acromegalics who still had normal ovarian function, and one acromegalic who had concomitant hyperparathyroidism. *Second*, that a prompt fall in serum phosphorus occurred in a few acromegalics who had received estrogen administered on the basis of

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† Lt. (j.g.) M.C., U.S.N.

the observations of Kirklin and Wilder(1). *Third*, examination of the literature revealed that growing children without exception have an elevation of the serum phosphorus, such elevation being roughly proportional to the

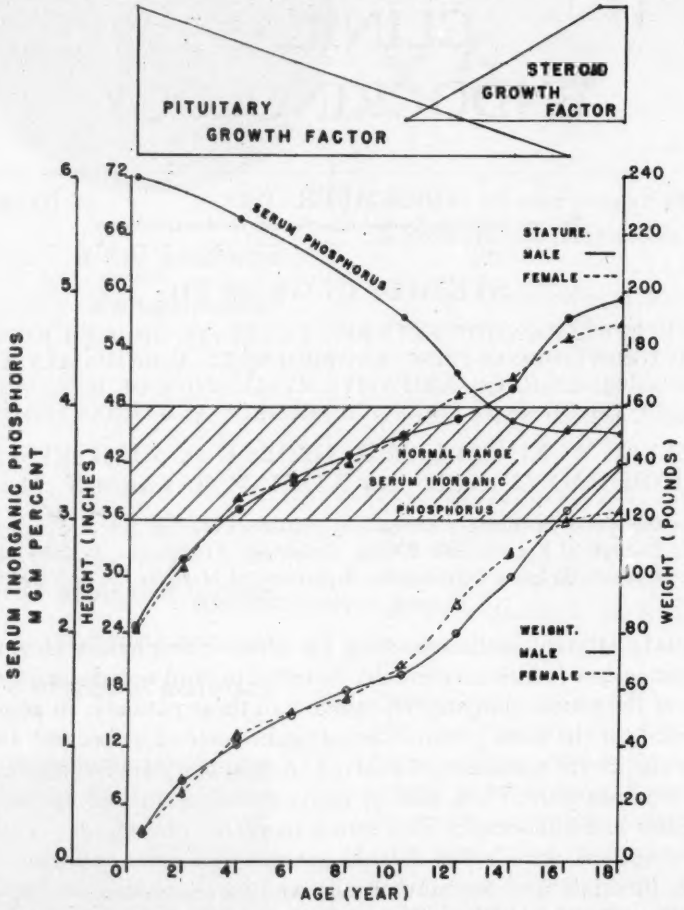


FIG. 1a. Normal growth, showing serum inorganic phosphorus relationship, and hormonal control (semi-diagrammatic).

prepubertal rate of growth, and that during the second (pubertal—"steroid induced") growth spurt, the serum phosphorus falls to normal levels(2). Some of these observations were reported in abstract form in 1946(3).

Based upon the preceding observations, and upon the fact that in the human, normal growth occurs in two" spurts," the following hypotheses

were constructed: *First*, that childhood growth, from an endocrine standpoint, is referable entirely to pituitary growth hormone, and that the serum inorganic phosphorus level (other phosphate regulating factors being normal) serves as an index of pituitary growth hormone activity. *Second*, that pubertal growth is induced by steroid growth-promoting factors from the gonads (and probably from the adrenal cortex), and that since the serum

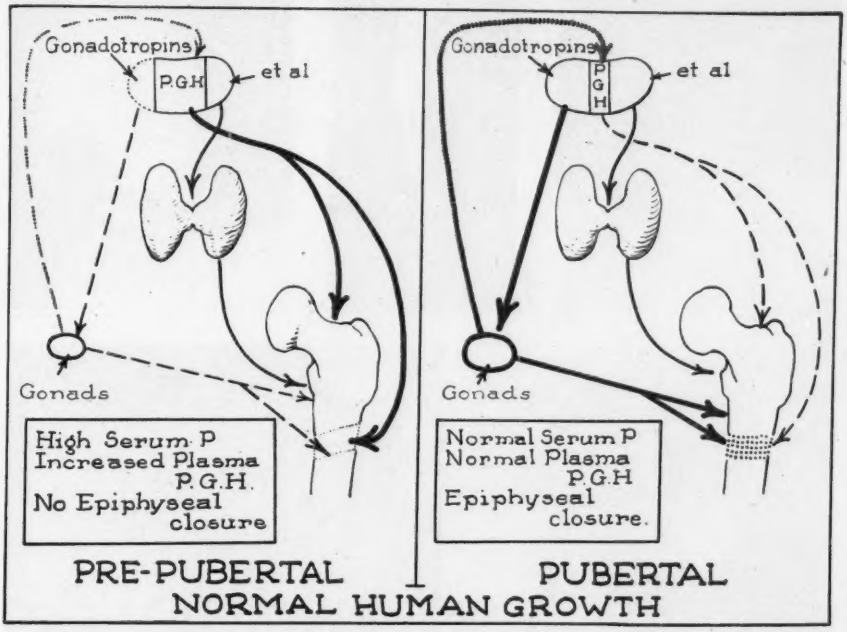


FIG. 1b. Normal growth, showing pre-pubertal and pubertal endocrine regulation (known and postulated). The arrow from gonad to pituitary in the pubertal phase implies inhibition.

phosphorus level falls to normal in rapidly growing adolescents as well as in acromegalics during estrogen administration, it is probable that such anabolic steroids inhibit the production of pituitary growth hormone.

Diagrammatically these concepts are shown in Figures 1a and 1b.

The major purposes of the studies here reported are threefold:

1. To document further the concept of the relationship between pituitary growth hormone production, and the level of the serum inorganic phosphorus.

2. To introduce data bearing upon the depressing effect on serum phos-

phorus and the inhibiting effect on pituitary growth hormone production of protein-anabolic androgens.[1]

FIG. 2. Patient SMA, aged 20 yrs. Acromegalic gigantism of five or more years' duration. A normal tall male and a normal hand are shown for comparison.

---

[1] We wish gratefully to acknowledge the receipt of generous supplies of testosterone compounds from Dr. Edward Henderson of the Schering Corporation; and also to express our thanks for supplies of Premarin from Ayerst, McKenna & Harrison.

3. To present certain balance studies which indicate that patients with untreated, *active*, progressive, acromegaly or gigantism, *on a diet adequate in calories and nutritionally optimal in other respects*, are *not* in negative calcium, phosphorus, or nitrogen balance. This latter point is in need of clarification, in view of conflicting reports in the literature(4).

## CLINICAL MATERIAL

Three individuals are considered: A young male acromegalic giant (SMA) aged 20 when first seen; a very typical male acromegalic aged 28 (MUR); and a female giantess without acromegaly, aged 22 (UKE). The last patient has been studied only superficially, as compared to the first two, but is presented for purposes of comparison with the male giant.

### *Protocols*

**Patient SMA (Fig. 2):**

A 20-year-old male; (on admission) height 79 inches; span 82 inches; weight, 248 pounds; shoe size, 14 D.

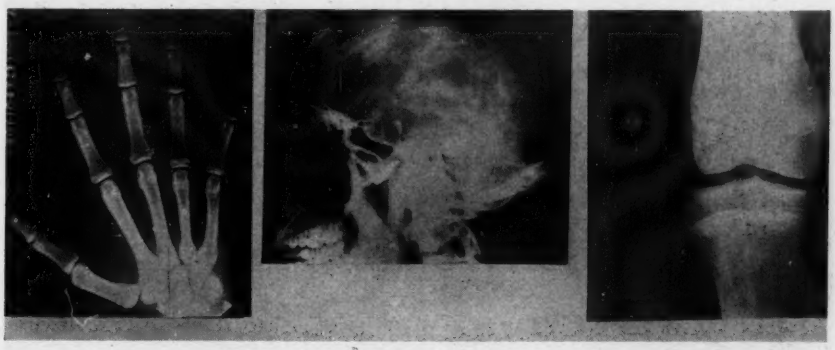

FIG. 3. Patient SMA—pertinent roentgenograms. The open epiphyses are particularly to be noted.

*Diagnosis*—Acromegalic gigantism.
*Age at onset*—Fifteen years or before, on the basis of serial photographs.
*Pertinent history and physical findings*—Excessive height, with continued growth, up to the time of this study.
Headaches—none.
Strength and energy—good, although less than formerly.
Subjective visual disturbance—none.
Mental activity—excellent.
Libido and potentia—probably decreased.

Gonadal development—left testis, atrophic (result of mumps orchitis); right testis, small, but possibly within the lower limits of normal.

Testicular histology—spermatogenesis present.

Axillary and pubic hair—grossly normal.

*X-ray examination*—(*Fig. 3*): Sella—markedly ballooned, and floor eroded. Epiphyses—many open. Spine—marked kyphosis and scoliosis.

*Visual fields*—slight encroachment.

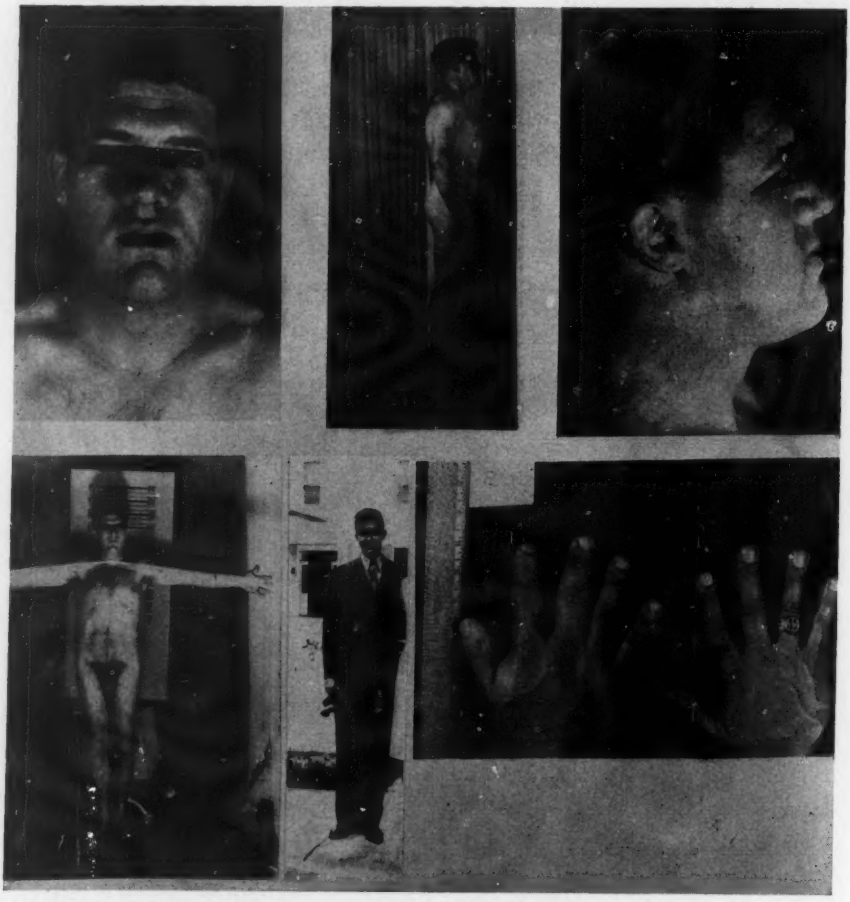

FIG. 4. Patient MUR, aged 28 yrs. Acromegaly of approximately five years' duration. Lower central photograph was taken two years before the onset of acromegaly. A normal hand is shown for comparison.

## Patient MUR (Fig. 4):

A 28-year-old male; weight, 188 pounds; height, 71 inches; span 72½ inches; shoe size 10½ EE.

*Diagnosis*—Acromegaly.

*Age at onset*—23 years.

*Pertinent history and physical findings*—Enlargement of face, hands and feet and increase in height from 69½ to 71 inches during the period 1944–1947.

Headaches—severe and frequent.

Strength—significantly decreased.

Visual disturbance—change in refraction, but no constriction of fields.

Mental activity—decreased drive.

Libido and potentia—almost completely absent.

Gonadal development—moderate decrease in size of testes and prostate.

FIG. 5. Patient MUR—Pertinent roentgenograms, showing typical acromegalic bone structure and enlargement of the sella.

Testicular histology—significantly decreased spermatogenesis (patient has one child born before the acromegaly started).

Axillary and pubic hair—probably normal (not measured quantitatively).

*X-ray examination*—(*Fig. 5*): Sella—markedly ballooned. Epiphyses—closed. Spine and hands—typical for acromegaly.

*Visual fields*—no encroachment.

## Patient UKE:

A 24-year-old female; weight, 203 pounds; height, 79¾ inches; span, 86 inches; shoe size, 13½.

*Diagnosis*—Gigantism.

*Age at onset*—Prepubertal (before 6 years of age.)

*Pertinent history and physical findings*—Symmetrical enlargement of entire skeleton; fingers tapering rather than broad.

Headaches—not of significant magnitude.

Strength—fair to good.

Visual disturbance—none.

Mental activity—normal.

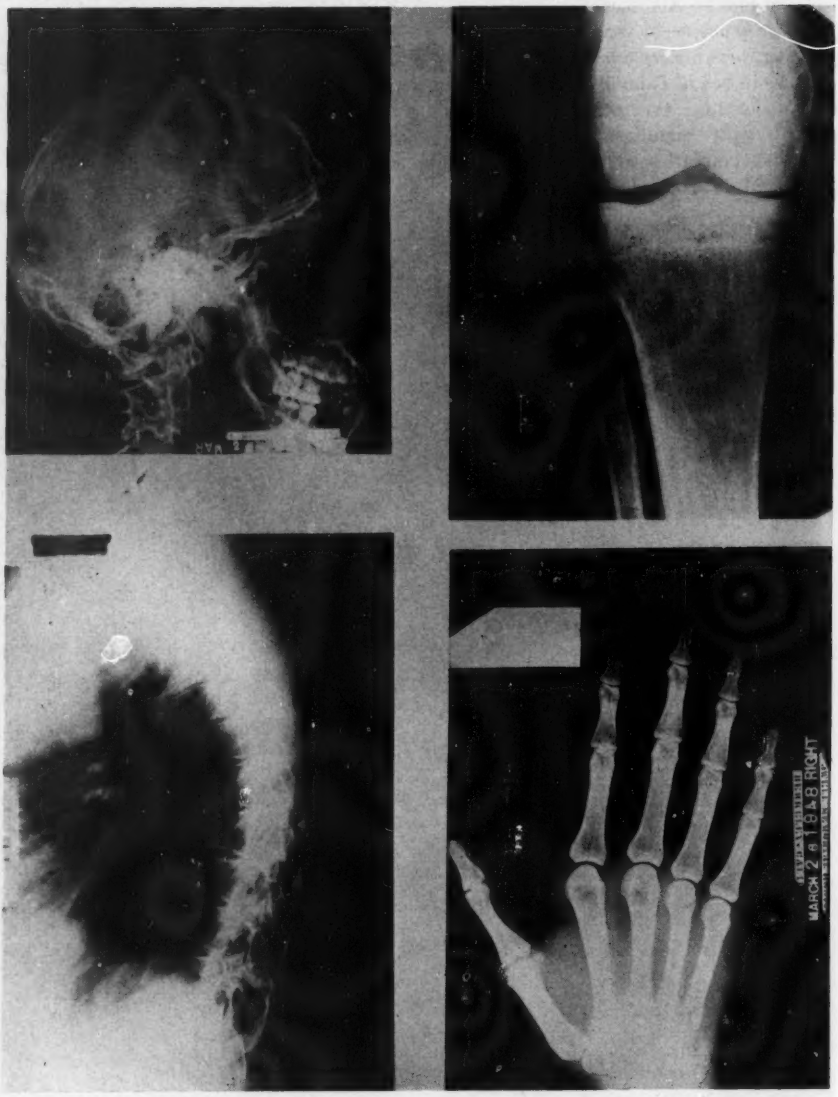


FIG. 6. Patient UKE (female), aged 22 yrs. Gigantism without acromegaly. Particularly to be noted are the normal sella, the closed epiphyses, and the tapering hands, as compared to patient SMA.

Breasts—small normal.
Genitalia—grossly normal.
Axillary, pubic, body and head hair—normal (not measured quantitatively).
Menses—*NONE* (*see* "Discussion").
Vaginal smear—"estroid" effect (to paraphrase Dr. Selye).
*X-ray examination*—(*Fig. 6*): Sella—normal. Epiphyses—closed. Spine—kyphosis and scoliosis.

### *Plan of Study*

The two males were studied in essentially identical fashion, as follows:

1. A long base line composed of calcium, phosphorus, and phosphatase determinations in serum, during a preliminary control period.
2. An initial 48-day balance study on similar, high protein diets, differing only on the basis of individual caloric requirements. Total nitrogen calcium and phosphorus were determined in urine and stool, throughout the study, together with uric acid, creatine, creatinine, and amino-nitrogen urine assays.
3. Determinations of calcium, phosphorus, and phosphatase in serum throughout the period of balance study.
4. Administration of 50 mg. of testosterone propionate in oil daily, intramuscularly, during the middle twenty-four days of the balance study.
5. Quantitative measurement of pituitary growth hormone content of plasma and urine, preceding, during, and following testosterone administration. (Because of technical difficulties, this has so far been performed only on the plasma, in patient SMA.)
6. Other hormonal assay procedures.
7. Serial visual field examinations.
8. Further "maintenance therapy" and studies as indicated by the results of the foregoing procedures.

With the exception of the last four items, all of these studies have been completed. For reasons presently to be given, a second 12-day balance study on a different diet, was carried out some weeks after the initial study. Since that time, both these men have received testosterone continuously, and in the case of patient MUR, estrogen as well, during part of his post-balance period of observation.

Patient UKE has been studied on an ambulatory basis, from the standpoint of serum phosphorus, gonadotropin excretion, and certain other objective endocrine criteria. We believe that she has "cured" herself, and will presently give the reason for that belief.

## METHODS

The methods used are described in detail in another paper(5).

## RESULTS

Because of the parallel nature of most of the studies in SMA and MUR, their data will be presented together, in graphic form.

### Serum calcium, phosphorus and phosphatase during initial study (Fig. 7)

*Phosphorus:* The normal range for serum inorganic phosphorus in this laboratory is 3 to 4 mg. per cent. The pre-treatment levels in these men are obviously high. The drop to normal levels during testosterone therapy, and the post-treatment rise, is striking.

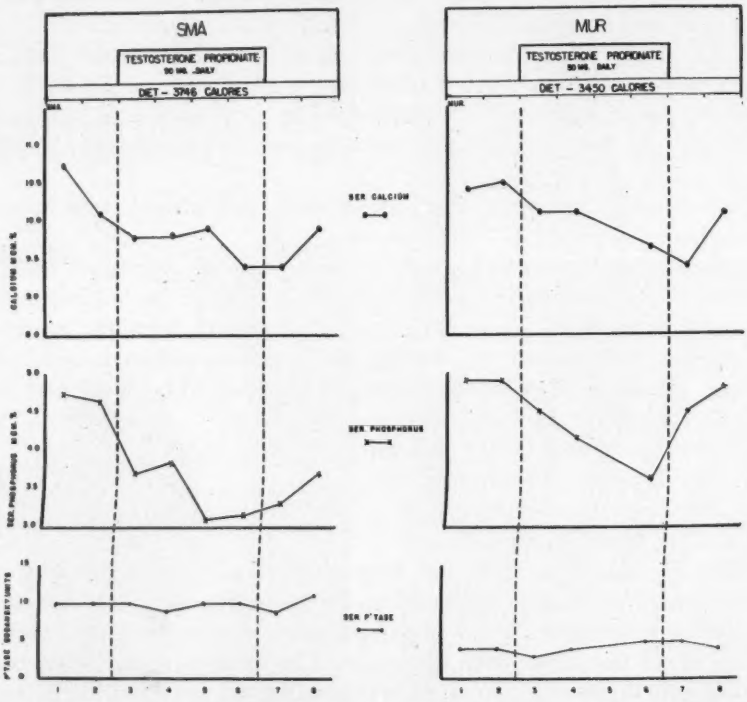


FIG. 7. Serum calcium, phosphorus, and phosphatase values in SMA and MUR during metabolic study. The high initial phosphorus values, and the fall in both patients in response to testosterone, are striking. Also to be noted is the high phosphatase in the giant SMA.

*Calcium:* The calcium values did not exceed the normal range of 9 to 11 mg. per cent but the parallelism of the calcium-phosphorus curves in relation to treatment is impressive.

*Phosphatase:* MUR, the acromegalic, had a normal value for phosphatase throughout, as had all other acromegalics we have studied. SMA, the ac-

romegalic giant on the other hand, had a consistent elevation of the alkaline phosphatase, which was in no way affected by treatment.

**Nitrogen-phosphorus balance (Fig. 8)**

These two ingredients of protein tissue are charted on a 15:1 scale, *i.e.*, approximately the ratio in which they occur in protein tissue. It will be noted that both men were initially in *positive* balance, which became more

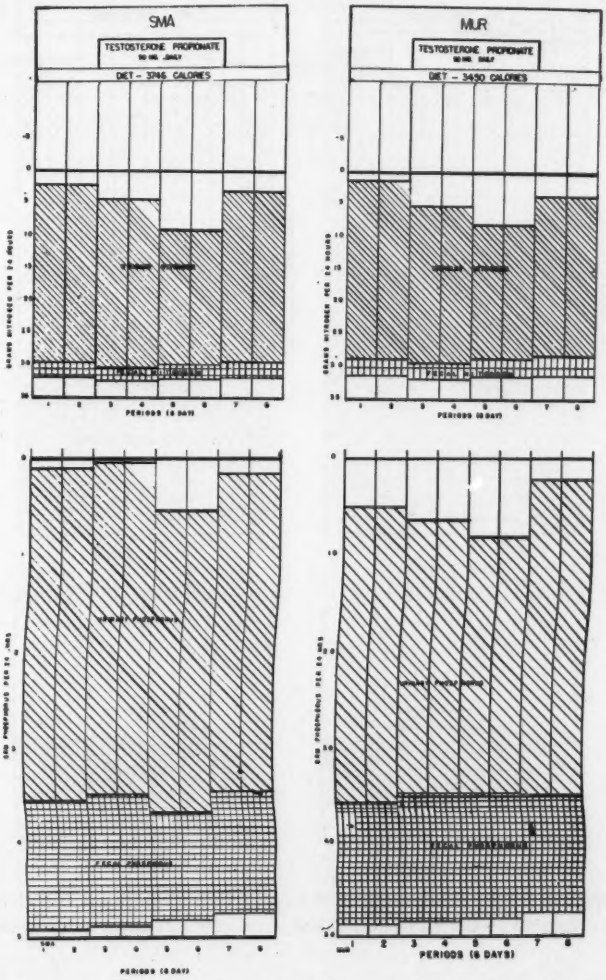


FIG. 8. Nitrogen-phosphorus balance in SMA and MUR. Positive balance occurred throughout, with increased nitrogen and phosphorus retention during administration of testosterone. The post-testosterone rebound was less than is usually noted.

positive during androgen administration and rebounded when treatment was stopped—but never became negative.

**Calcium-phosphorus balance (Fig. 9)**

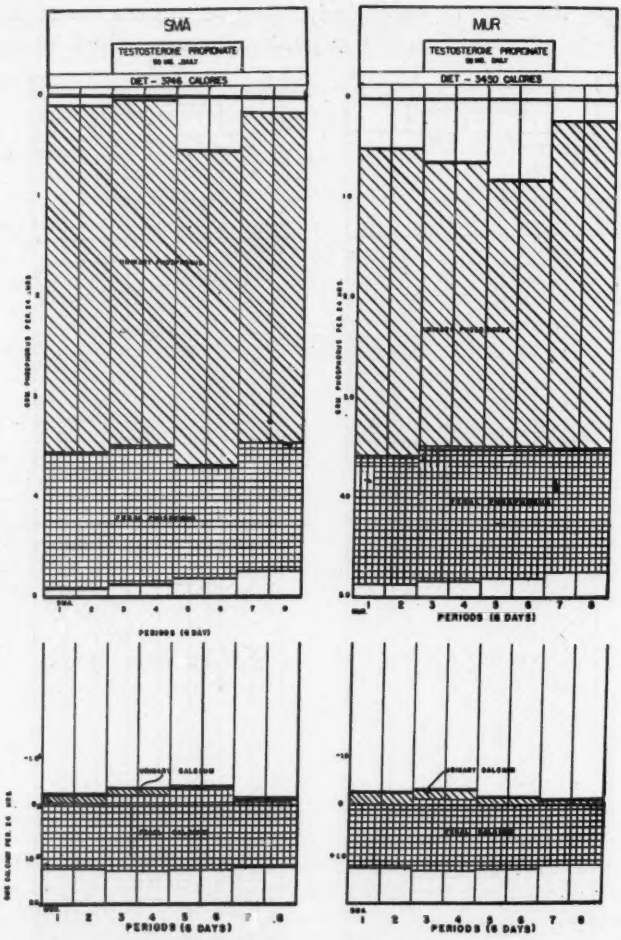


FIG. 9. Phosphorus-calcium balance in SMA and MUR. The negative calcium balance is referable to the large amount of stool calcium and phosphorus.

The findings, at first glance, are paradoxical—a strongly positive phosphorus balance, with a negative calcium balance. More careful observation brings out three things:

1. A very high phosphorus intake and high phosphorus content of the stool.
2. A very high stool calcium.
3. A low urinary calcium, which diminished still further during testosterone administration. The high phosphorus intake is accounted for by a high yeast content in the diet. On a more usual diet, of relatively low phosphorus content, the calcium balance became strongly positive (Figs. 12a and 12b).

**Creatine and creatinine excretion (Fig. 10)**

Worthy of comment is the high urinary creatine in patient MUR, with a prompt fall to normal during administration of androgen. This may coincide with the greater evidence of gonadal insufficiency in this man, as compared to SMA.

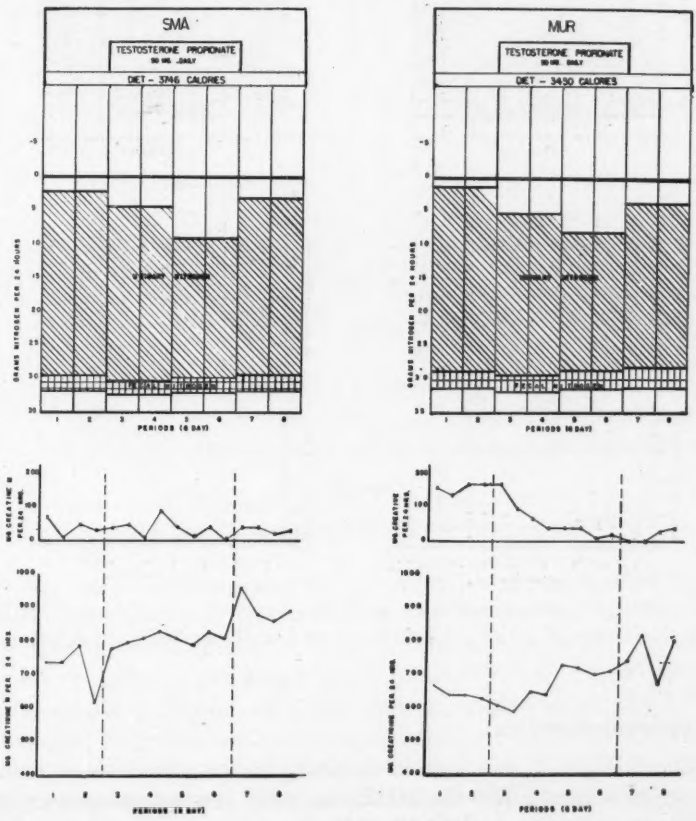


FIG. 10. Creatine-creatinine *nitrogen* excretion in SMA and MUR. The high pre-testosterone creatine excretion in MUR probably related to his hypogonadism.

**Uric acid and amino nitrogen excretion (Fig. 11)**

The increased net excretion of both these protein catabolites during a period of general and profound protein anabolism impresses one initially as being difficult to explain physiologically.

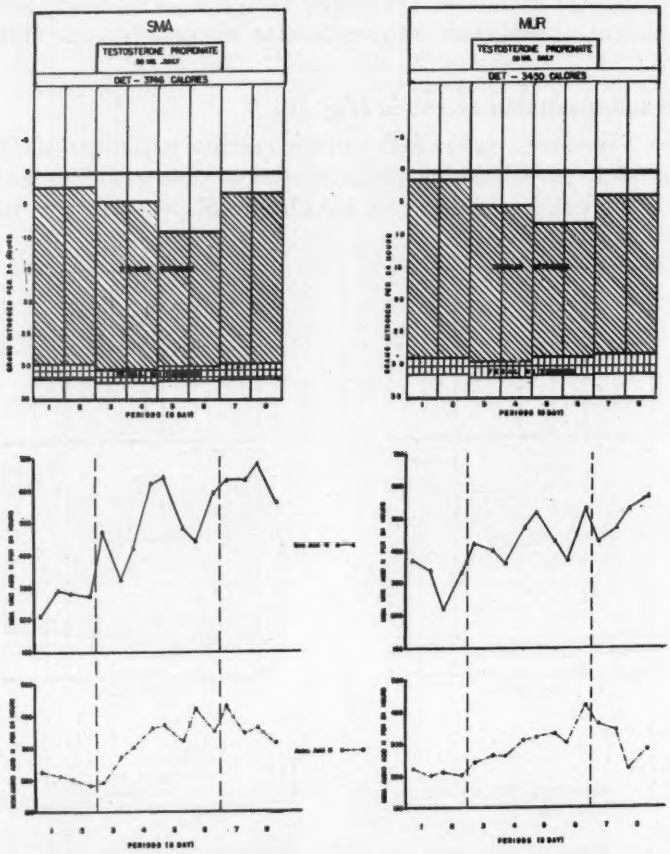


FIG. 11. Uric acid *nitrogen* and amino acid *nitrogen* excretion in SMA and MUR. The increased elimination of amino acids during a profoundly anabolic period, seems paradoxical.

**17-Ketosteroid excretion**

In patient SMA, 17-ketosteroid excretion in the urine was consistently within upper normal limits. In MUR, the daily pre-testosterone excretion averaged somewhat more than 30 milligrams.

**Urinary gonadotropin**

SMA had a normal urinary gonadotropin titer. MUR had less than 12 mouse units per twenty-four hours. Lower values (pre-treatment) were impossible to determine because of some toxic factor in the urinary extract.

**Pituitary growth hormone in plasma and urine (Table 1)**

As previously noted, it was planned to run pituitary growth hormone assays on plasma and urine, preceding and during androgen administration, using the method described by Evans, Simpson, Marx and Kibrick (6).

TABLE 1. PITUITARY GROWTH HORMONE ACTIVITY OF HUMAN PLASMA AS ASSAYED ON PROXIMAL EPIPHYSEAL CARTILAGE OF TIBIA IN HYPOPHYSECTOMIZED FEMALE RATS

| Plasma | Daily dose | No. of rats | Width of uncalcified cartilage | |
|---|---|---|---|---|
| | | | Mean | Difference from control |
| | mg. | | $\mu$ | $\mu$ |
| Patient SMA (Pre-testosterone) | 60 | 4 | 210 | + 65 |
| | 100 | 5 | 246 | +101 |
| | 200 | 5 | 270 | +125 |
| Patient SMA (Post-testosterone) | 200 | 5 | 177 | + 32 |
| Normal | 200 | 5 | 158 | + 13 |
| Control | 0 | 6 | 145 | 0 |

Conclusion: 100 mg. of SMA's plasma (pre-treatment) contain about 0.020 mg. growth hormone.

It will be noted from reference to Figure 7, that the plasma pituitary-growth-hormone content and inorganic phosphorus content have behaved in a parallel fashion.

Such an assay was performed on lyophilized plasma obtained from SMA preceding therapy, and again at the end of twenty-four days of treatment with testosterone propionate (Table 1). The results are not equivocal. The pituitary growth hormone content of the plasma, before androgen therapy, was markedly increased over that present in plasma obtained from normal adults. Following androgen administration, the pituitary growth hormone content fell to normal levels.

The plasma obtained before treatment in MUR was destroyed as the result of an accident in the course of lyophilization.

In both men the urinary extracts, prepared by precipitation with ammonium sulfate, followed by dialysis, proved to be too toxic to permit of assay in hypophysectomized animals.

**Visual field changes**

No defect was found in MUR. SMA did show evidence of encroachment

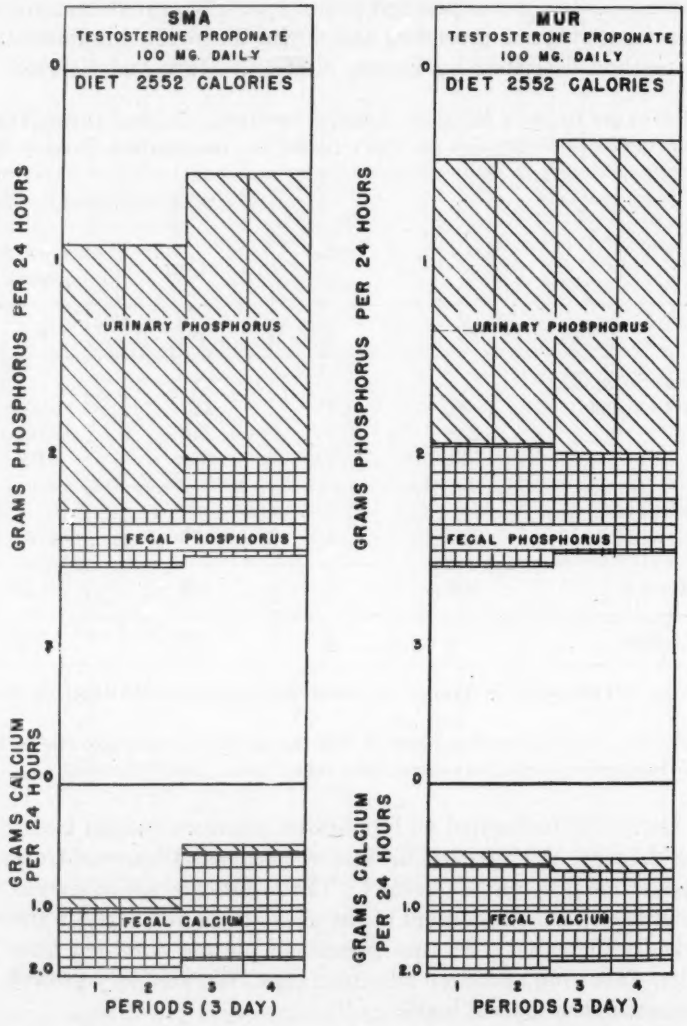


FIG. 12a. Second nitrogen-phosphorus balance study in SMA and MUR—note strongly positive balance throughout.

which, after nine months on androgen therapy, had advanced slightly. This advance may be referable to inadequate dosage during part of the study.

Following the studies just described these men left the hospital for a period of one month, during which time they took 100 mg. of methyl testosterone daily. On their return, serum phosphorus values in both were found to be extremely high. When the methyltestosterone was stopped, and

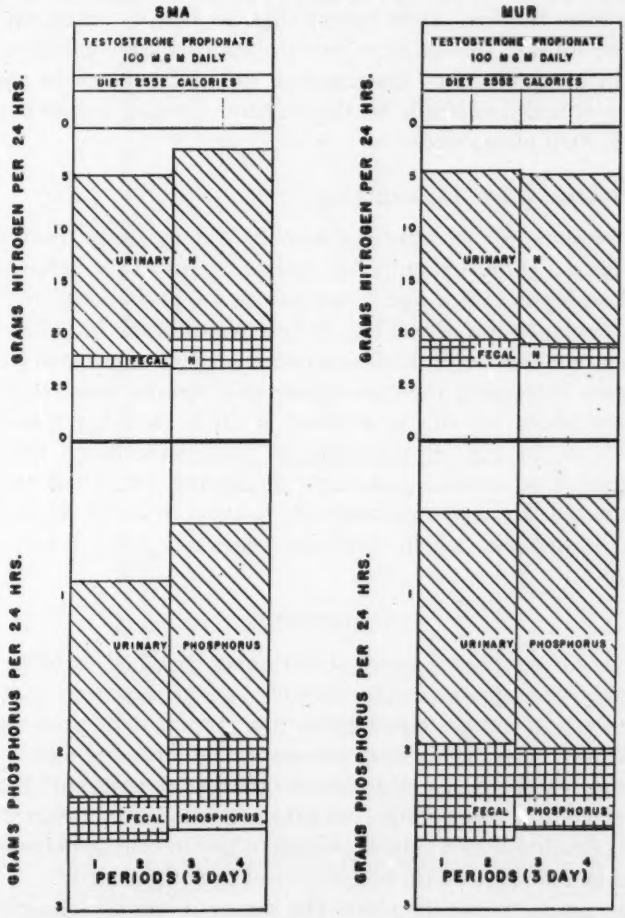


FIG. 12b. Second phosphorus-calcium balance study in SMA and MUR—the normal relationship between calcium and phosphorus indicates that the negative calcium balance in the initial study was referable entirely to an abnormal phosphate content of the diet.

testosterone propionate resumed, the serum phosphorus in SMA promptly fell to normal but that in MUR was less responsive as compared to results during the original course of testosterone administration. Symptomatically, SMA did not have any complaints; MUR had a return of headaches during methyltestosterone therapy and a rapid and complete disappearance of headaches when testosterone propionate was resumed.

A second balance study was instituted shortly after resumption of testosterone propionate (Figs. 12a and 12b). Nothing about this differs remarkably from the first study except that, as already noted, on a normal phosphorus intake, the calcium balance was strongly positive. We feel justified in assuming that the negative calcium balance in the original study was entirely referable to the calcium binding power of the huge amount of stool phosphorus.

**Further Studies (Figs. 13a and 13b)**

For a 5-month period after the second balance study, both men were followed from a clinical standpoint, and in regard to the behavior of their serum phosphorus. SMA had a normal serum phosphorus two months after the implantation of 900 mg. of free testosterone in pellet form, but it was apparent that MUR had become refractory to androgen alone in any dosage used. Increasing amounts of estrogen (testosterone remaining constant) were added. As this is written, MUR is receiving a large dose of estrogen[2] and 25 mg. of testosterone propionate daily. On this combined therapy no evidence of any "feminizing effect" of the estrogen has been noted. He is symptomatically normal in every respect, and has a serum phosphorus which fluctuates between normal and abnormal values.

## DISCUSSION

Methods for the direct assay of hormones in blood or urine are obviously highly desirable but unfortunately, up to this time, quite difficult and complex. Of almost equal value are quantitative procedures based upon a known relationship between a specific hormonal agent, and some other more readily measurable blood or urine constituent. Examples of this latter approach are serum calcium and phosphorus values in hyper- and hypoparathyroidism; blood glucose in hyper- and hypoinsulinism and blood iodine and cholesterol in hyper- and hypothyroidism.

To this category can be added the serum inorganic phosphorus, as a diagnostic agent, and as an agent for the evaluation of the therapy of acromegaly. In support of this statement are the facts just reported, namely:

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[2] 0.15 mg. of ethinyl estradiol.

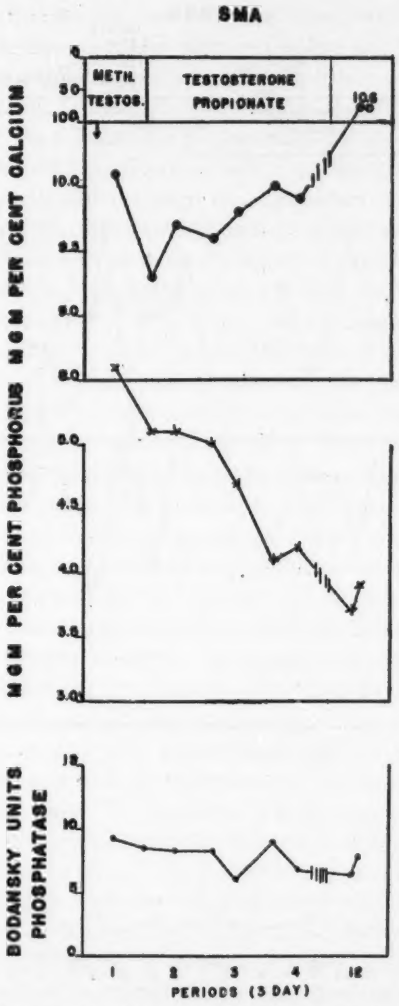


FIG. 13a. Further calcium, phosphorus and phosphatase studies on the serum in SMA. Of note is the lack of phosphorus response to methyltestosterone. The final two normal values relate to the effect of 900 mg. of free testosterone pellets implanted approximately two months previously. The gradual downward trend of the phosphatase probably refers to progressive epiphyseal closure.

Elevation of the serum phosphorus in untreated active acromegaly.

Elevation of the plasma pituitary growth hormone content in untreated active acromegaly.

A parallel fall to normal of both these entities in the course of treatment with androgen.

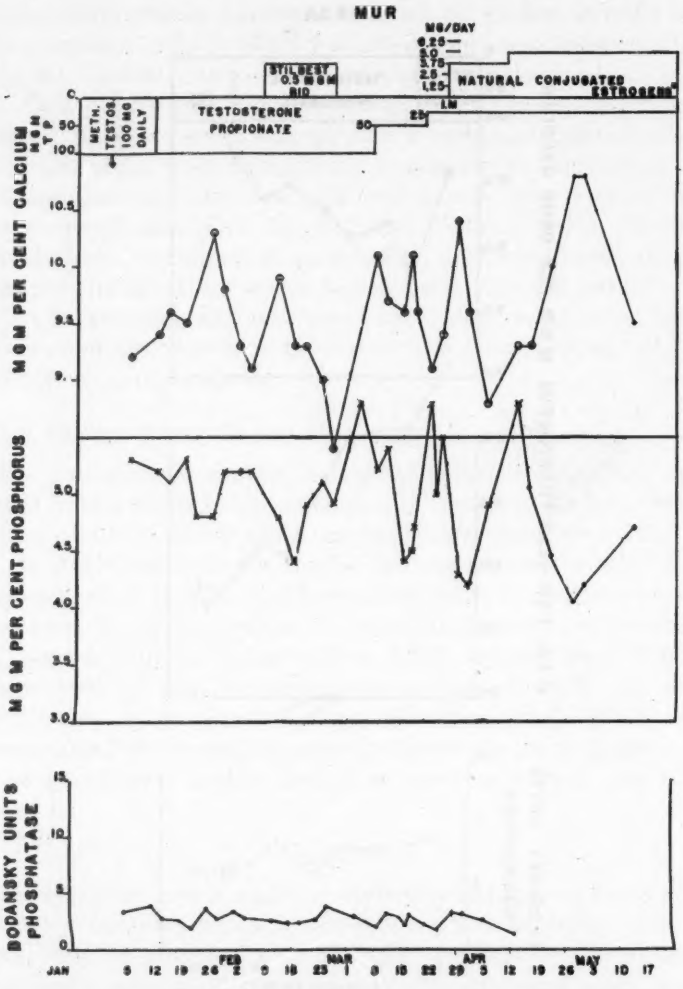


FIG. 13b. Further calcium, phosphorus, and phosphatase studies on the serum in MUR. After the initial interruption of treatment, androgen failed to produce the desired result. Empirical combinations of androgen-estrogen are under study.

Still further evidence is present in unpublished work of Li, in which has been shown significant elevation of the serum phosphorus in hypophysectomized rats during the course of pituitary growth hormone administration

The relationship of these findings to the physiology of normal growth, as previously noted, is obvious.

As a corollary to the above, one is equally justified in concluding that anabolic steriod-hormone therapy has real value in the management of patients with acromegaly and gigantism. Whether androgen, estrogen, combinations of both or the use of other steroid hormones, as yet untried, will prove to be the "best" therapy in the disease is unknown. It may well be that considerable individualization will continue to be necessary, and that some pituitary adenomata may be completely refractory, as in the case of tumors generally. The development of a partially refractory state in MUR, after therapy had been temporarily stopped, may indicate the desirability of uninterrupted therapy over prolonged periods of time in those individuals who make a satisfactory initial response.

Brief comment on the lack of "feminizing effect" of the large dose of estrogen is in order. This probably represents a peripheral neutralization mechanism on the part of the concomitantly administered androgen. This interpretation, if correct, is important in view of the similar complementary action of the two hormones in such conditions as osteoporosis(7).

At the moment, adequate initial therapy might properly be regarded a from 25 to 50 mg. of testosterone propionate daily in the male, and the equivalent of from 0.05 to 0.3 mg. of ethinyl estradiol daily in the female, using the serum phosphorus as an index of effectiveness of therapy. Lest the effects of therapy be as undesirable as the disease itself, estrogen alone in the male, and androgen alone in the female, are contraindicated. Also contraindicated, at least for the present, is the use of methyltestosterone (Figs. 13a and 13b).

*Reports of negative calcium, phosphorus, and nitrogen balances, in patients with a disease which is characterized by excessive growth, are perplexing, to say the least.* From our own data, we are sure that such a situation does not exist in patients with unquestionably active acromegalic processes on an adequate diet. Two possible explanations could account for the negative balances noted by other observers(4): If the acromegalic studied no longer had an actively secreting tumor, he could conceivably be in a slow "rebound" phase; if, on the other hand, an active acromegalic received less than an iso-caloric diet (and such individuals have high energy requirements), he could readily be in negative balance during the period of study. The importance of this factor in the production of a positive protein balance has recently been shown in metabolic studies in post-traumatic individuals (8).

Another observation of some interest in these men relates to the post-testosterone findings. In the majority of such studies which have been reported in nonacromegalics, a rebound to negative levels is noted when steroid administration is discontinued. In Figure 8, it will be noted that both men were in positive balance throughout, the post-testosterone level being

essentially identical with the pre-treatment values. Conceivably this may mean that resumption of pituitary growth hormone secretion inhibits to some degree the usual post-testosterone tissue breakdown.

Comparison of SMA and UKE brings out some rather striking differences despite the almost identical ages and heights of the two individuals. It will be recalled that Albright had postulated a high serum phosphatase in acromegaly, but failed to find it in any instance. The only exception to this rule, in our experience, is the acromegalic giant SMA. Since his major point of difference from the rest of the patients whom we have studied over the past ten years is the possession of open epiphyses, it seems reasonable to conclude that the greater amount of osteoblastic activity referable to such epiphyseal growth explains completely this isolated observation. We assume that the serum phosphatase will return to normal when epiphyseal closure is complete. Such a gradual decrease is apparently already in progress. Substantiating this interpretation further are the findings of a normal phosphatase and closed epiphyses in the giantess, UKE.

The matter of epiphyseal closure in the giantess also requires explanation. Since, as noted by Talbot and Sobel(9) in the human, it seems probable that epiphyseal closure will occur in response to steroid hormone stimulation but not to pituitary growth hormone, it follows that UKE has produced considerable amounts of growth-promoting steroids. This assumption is in accord with the findings of essentially normal genital development. The history of complete amenorrhea was the only perplexing part of the picture, but this has been resolved. A vaginal smear showed a picture compatible with the presence of estrogen. The administration of 5 mg. of progesterone daily for five days resulted in a "normal" period, the first in her life. A second flow occurred four weeks later in response to similar dosages of progesterone. We think it probable that she has almost if not entirely cured herself with endogenous steroids; although, if her serum phosphorus continues slightly elevated, we shall consider it an indication for supplemental steroid "inhibition therapy." In her case this would involve the determination of the effect of progesterone alone.

Returning to theoretical matters—the paradox of increased total nitrogen retention, coupled with increased urinary uric acid and amino-nitrogen, calls for explanation. It this is a usual testosterone effect, we have been unaware of it. Whether usual or not, one must conclude that in these two men certain nucleoproteins and amino acids (probably resulting from the catabolized nucleoprotein) are in excess supply in the construction of the protoplasm which is induced by testosterone administration. The only other possible explanation which would occur to us, would be an effect of the administered testosterone on the renal tubules resulting in decreased

reabsorption of both these substances. Both hypotheses will be investigated.

A final word of caution concerning practical therapeutics: significant evidence of optic nerve pressure, progressing despite medical treatment, should be regarded as a specific indication for surgery. Aside from such indication, we believe that steroid hormone therapy may be and should be used over prolonged periods of time under proper supervision, without inclusion of roentgen ray therapy. Simultaneous use of both, obviously makes evaluation of the effectiveness of either impossible. When very large dosage of steroid hormone is necessary, the patient should be informed of the possibility of permanent gonadal impairment, insofar as fertility is concerned. This result is unlikely but in any event, from a genetic standpoint, would be desirable in such individuals.

## SUMMARY

1. Active acromegaly is characterized by a high serum content of inorganic phosphorus, and by a high plasma content of pituitary growth hormone.

2. Androgenic (and estrogenic) steroids will produce a fall to normal of the serum inorganic phosphate, and of the plasma growth hormone levels.

3. Evidence is presented which indicates that the drop in the level of serum phosphorus coincides with a decrease in pituitary growth hormone production.

4. Patients with active acromegaly and gigantism on an adequate diet are, as one would expect, in positive calcium, phosphorus, and nitrogen balance.

## *Acknowledgment*

Acknowledgment is made to Dr. Herbert M. Evans, Dr. Miriam E. Simpson, and other members of the staff of the Institute of Experimental Biology, University of California, for their kind advice during the progress of this work.

## REFERENCES

1. Kirklin, O. L., and Wilder, R. M.: Follicular hormone administered in acromegaly, *Proc. Staff Meet., Mayo Clin.* **11**: 121–125 (Feb. 19) 1936.
2. Stearns, G., and Warweg, E.: Studies of phosphorus of blood; partition of phosphorus in whole blood and serum, serum calcium and plasma phosphatase from birth to maturity, *J. Biol. Chem.* **102**: 749–765 (Oct.) 1933.
3. Reifenstein, E. C., Jr.; Kinsell, L. W., and Albright, Fuller: The effect of estrogen therapy in acromegaly with observations on the use of the serum phosphorus level as an index of pituitary growth hormone activity, Proc. Am. Soc. for Clin. Investigation, *J. Clin. Investigation* **25**: 932, 1946.

4. (a) MEDIGRECEANU, F., and KRISTELLER, L.: General metabolism with special reference to mineral metabolism in a patient with acromegaly complicated with glycosuria, *J. Biol. Chem.* **9**: 109–120, 1911.
   (b) BERGEIM, O.; STEWART, F. T., and HAWK, P. B.: A study of the metabolism of calcium, magnesium, sulfur, phosphorus, and nitrogen in acromegaly, *J. Exper. Med.* **20**: 218–224, 1914.
   (c) SCRIVER, W. DE M., and BRYAN, A. H.: Observations upon the calcium and phosphorus metabolism in a case of acromegaly showing marked osteoporosis, *J. Clin. Investigation* **14**: 212–219 (March) 1935.
   (d) BAUER, W., and AUB, J. C.: Studies of calcium and phosphorus metabolism; influence of the pituitary gland, *J. Clin. Investigation* **20**: 295–301 (May) 1941.
5. KINSELL, L. W., MICHAELS, G. D., and others: Protein balance studies in patients with liver damage. I. The role of diet. To be published.
6. EVANS, H. M.; SIMPSON, M. E.; MARX, W., and KIBRICK, E.: Bioassay of the pituitary growth hormone. Width of the proximal epiphysial cartilage of the tibia in hypophysectomized rats, *Endocrinology* **32**: 13–16 (Jan.) 1943.
7. ALBRIGHT, F.: The effect of hormones on osteogenesis in man, *Recent Progr. Hormone Research* **1**: 293–353, 1947. .
8. WERNER, S. C.: Some effects upon nitrogen balance of the independent variation of protein and calories in man, Proc. Am. Soc. for Clin. Investigation, *J. Clin. Investigation* **27**: 561 (July) 1948.
9. TALBOT, N. B., and SOBEL, E. H.: Certain factors which influence the rate of growth and the duration of growth of children, *Recent Progr. Hormone Research* **1**: 355–369, 1947.

# ABSORPTION AND EXCRETION OF CHORIONIC GONADOTROPIN ADMINISTERED INTRAMUSCULARLY IN WOMEN*

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IT HAS been shown that daily doses of 10,000 international units (I.U.) of chorionic gonadotropin prolong the life of the corpus luteum in women (1). In that study, it was also observed that urinary excretion of the gonadotropin was sufficiently high to give a positive Aschheim-Zondek reaction. The factors concerned in the absorption and excretion of the injected hormone were sufficiently obscure to justify an attempt to determine whether delaying absorption might prolong the effectiveness of treatment.

## MATERIALS AND METHODS

Women on the gynecologic ward who were waiting for elective surgical procedures were selected as test subjects. Chorionic gonadotropin (Antuitrin-S) was given as a single intramuscular injection (10,000 I.U.—either in aqueous solution, mixed with an emulsifying agent (Emulgen) or in oil and 1 per cent wax (A.P.L.). Urine was collected as successive 12-hour specimens for periods of 48 to 120 hours. The chorionic hormone concentration in this urine was determined by injection into immature female rats. The end point of the assay was the presence or absence of corpora lutea in the ovaries of the rats 96 hours after the first injection.

In preliminary tests, it was noted that injection of 3 cc. of urine (1 cc. per day) gave inconsistent results and that dilute specimens frequently resulted in negative tests. Computing the time equivalent of a 3 cc. urine volume showed that, in general, tests were positive when this volume represented three or more minutes' output of urine. The assays reported in this study were made with dilutions or concentrations of urine representing 1, 3 or 6-minute urine volumes per rat. After injecting urine volumes representing a 3-minute output, chorionic hormone was uniformly present in the urine as long as 48 hours after the injection, irrespective of the medium employed. The period of observation was then extended to 96 and 120 hours.

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EXPERIMENTAL

Six to twelve hours after giving the gonadotropin in aqueous solution, approximately 1 rat unit was excreted each 3 minutes (Fig. 1). From the twenty-fourth to the forty-eighth hour, there was a rat unit excreted every

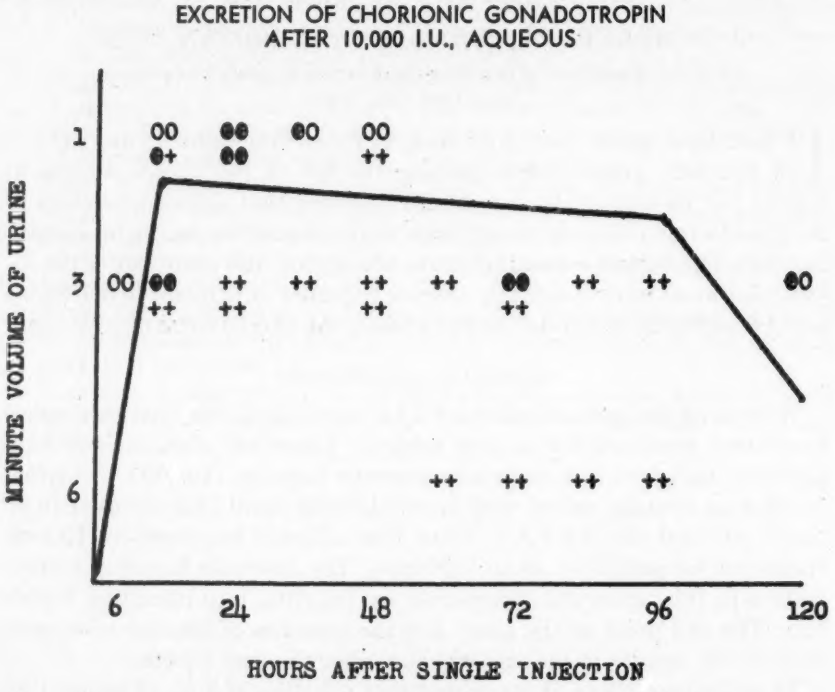


FIG. 1. Graphic representation of the results of gonadotropic assay of urine samples obtained after a single injection of chorionic gonadotropin in aqueous solution. The plus signs denote positive rat assays, the zeros denote negative assays and the plus sign within the zero represents a partial response in the test rat. The partial response was characterized by a patent vagina, a distended uterus and possibly some cystic change in the ovarian follicles.

1 to 2 minutes. At least 1 rat unit was excreted every 3 minutes until the ninety-sixth hour after injection when the rate of excretion diminished.

When the chorionic hormone was given in oil and wax its appearance in the urine was delayed so that it was later than the twelfth hour before the excretion rate equalled 1 rat unit per 3 minutes (Fig. 2). The 1-minute urine assays were uniformly negative indicating that the excretion rate was never as high as after injection in an aqueous solution. A 3-minute urine

volume contained only 1 rat unit from the sixtieth to the seventy-second hour and was negative at 96 and 120 hours. This indicates that the release of hormone from the injection site was so slow that the excretion levels were neither as high, nor as prolonged, as with the aqueous solution.

When the hormone was given in an emulsion of oil and cholesterol (Emulgen), the excretion rate was very similar to that obtained when wax

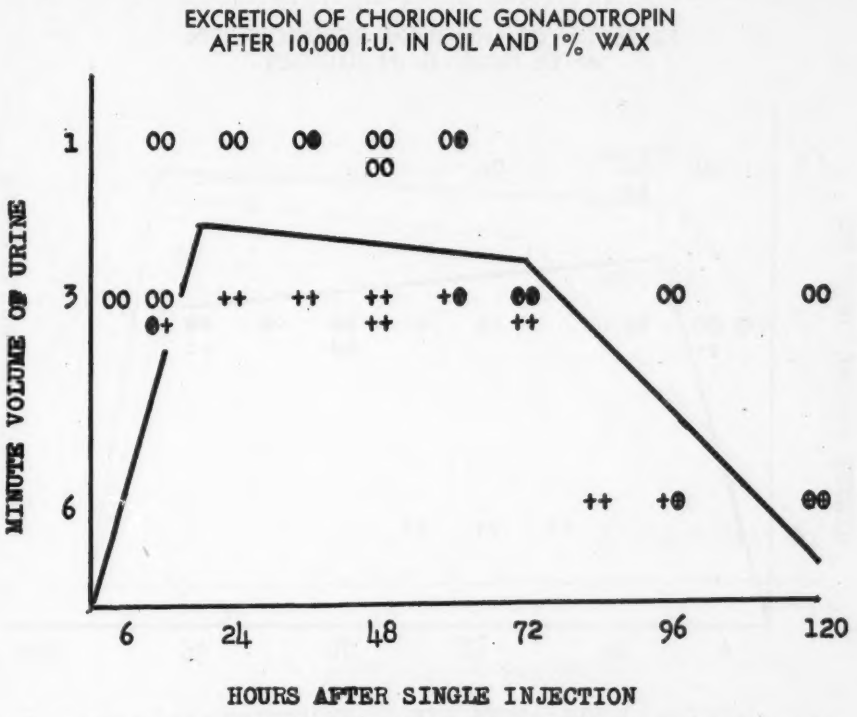


FIG. 2. Graphic representation of the results of gonadotropic assay of urine samples obtained after a single injection of gonadotropin in oil and 1% wax.

and oil were employed (Fig. 3). Again, its initial appearance was delayed and there was an apparently lower excretion rate at 72 to 96 hours.

In summary, chorionic hormone administered in three different media was excreted at similar rates (Fig. 4). When an aqueous solution was used, the onset of excretion was earlier but the rates of excretion from the twenty-fourth to the sixtieth hour were not significantly different. The prolonged higher excretion rate of gonadotropin administered in aqueous solution would indicate that there is probably no advantage of using an oily medium to delay absorption at the injection site.

The continued excretion of chorionic hormone for four or five days might be anticipated from earlier observations that the Aschheim-Zondek test may be positive on urines obtained several days postpartum. Crew (2) reported positive Friedman tests on urines obtained on the third day after delivery. The authors recently found that there was at least 1 rat unit of chorionic gonadotropin in 3 cc. of blood serum on the fifth post-

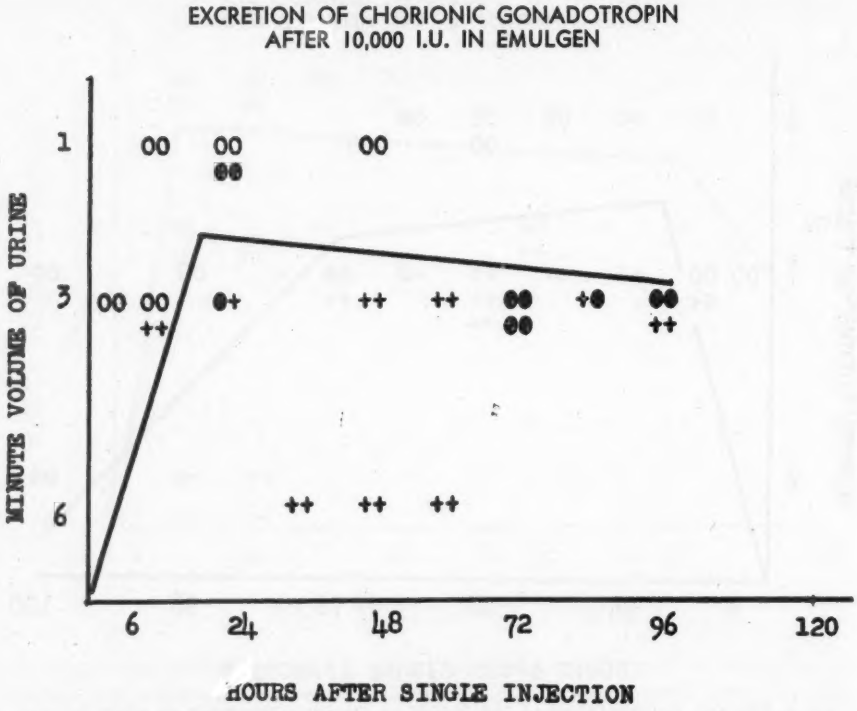


FIG. 3. Graphic representation of the results of gonadotropic assay of urine samples obtained after a single injection of chorionic gonadotropin in Emulgen.

partum day. Thus, even after loss of the placental source of the hormone, it takes several days for this protein hormone to be eliminated from the blood stream. Since there is no known storage depot in the puerperal patient, the prolonged excretion is probably a reflection of the relatively slow rate at which this hormone is filtered through the kidney.

If the total excretion of hormone, injected as an aqueous solution, is estimated for the 96-hour observation period, on the basis of 1 rat unit every 2 minutes from the twelfth to the thirty-sixth hour and 1 rat unit

every 3 minutes from the thirty-sixth to the ninety-sixth hour, approximately one-half of the injected hormone can be recovered. Allowing for some excretion at lower rates before and after this period, there seems to be relatively little destruction or utilization of the hormone in the body.

Friedman and Weinstein (3) injected chorionic hormone into normal men and tested the urine for gonadotropin. The dose they used was about

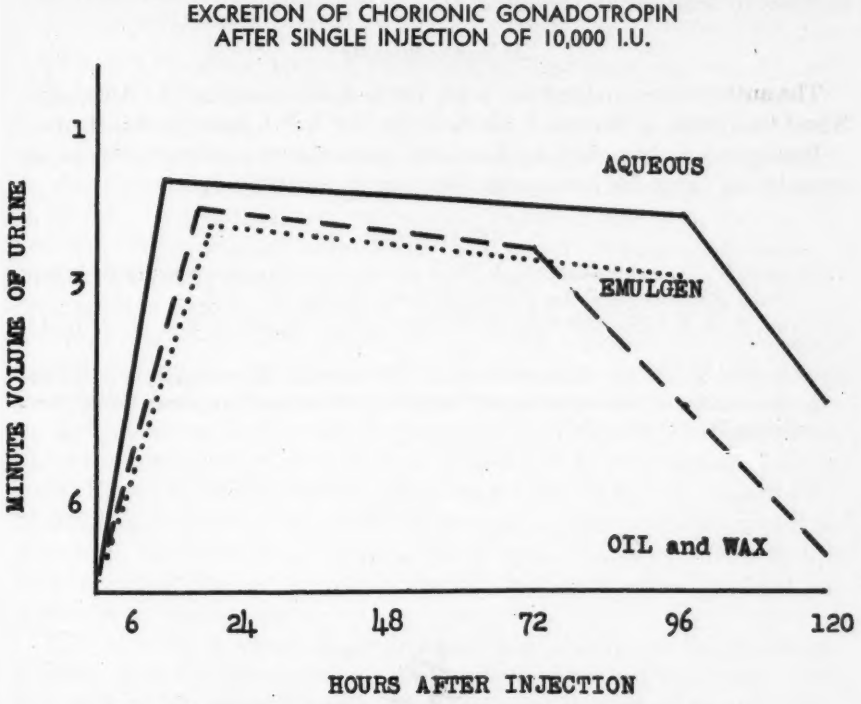


FIG. 4. Summary graph to compare the excretion rates of chorionic gonadotropin after injection in three different media.

one-tenth (480 R.U., roughly 1,000 I.U.) that given to the women in this study. They found no significant increase in urinary gonadotropin even when extracts representing several hours of urine excretion were given to the test rabbits. The chorionic hormone preparation used in their study was relatively impure and was highly pyrogenic. Possibly the tissue reaction tended to localize the hormone and delay its absorption.

## SUMMARY AND CONCLUSIONS

When chorionic hormone was incorporated into oily media and injected intramuscularly there was a definite delay in its appearance in the urine.

However, the excretion levels did not rise so high or persist so long as when the hormone was injected in aqueous solution. The fact that the hormone is a protein that filters slowly through the kidney seems to obscure any advantage that might be obtained by delayed absorption. For therapeutic purposes, the prolonged excretion of the hormone after a single injection in aqueous solution would indicate there is no advantage in using an oily medium to delay its absorption at the site of injection.

*Acknowledgments*

The authors are indebted to Parke, Davis & Company for the Antuitrin-S and to Ayerst, McKenna & Harrison for the A.P.L. used in this study.

Emulgen was furnished by Lakeside Laboratories and was used as an emulsifying agent for an aqueous solution of Antuitrin-S.

REFERENCES

1. Brown, W. E., and Bradbury, J. T.: A study of the physiologic action of human chorionic gonadotrophin, *Am. J. Obst. & Gynec.* **53**: 749–757, 1947.
2. Crew, F. A. E.: The Aschheim-Zondek test in the puerperium, *Brit. M. J.* **1**: 363, 1936.
3. Friedman, M. H., and Weinstein, G. L.: The excretion of gonadotropin by normal human males after the ingestion and injection of extracts of pregnancy urine, *Endocrinology* **21**: 489–494, 1937.

# EXCRETION STUDIES ON THIOURACIL AND ITS 6-BENZYL, 6-n-PROPYL AND 6-METHYL DERIVATIVES IN MAN*

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AMONG the derivatives of thiouracil studied quantitatively by Astwood, Bissell and Hughes (1) for antithyroid activity in rats, 6-benzylthiouracil was found to be one of the most active compounds. On the basis of reduction in thyroid iodine concentration and to a lesser extent on the degree of thyroid enlargement following administration of the drug in the diet for ten days, benzylthiouracil was estimated to be 10 times as active as thiouracil and only slightly less potent than propylthiouracil. Methylthiouracil was estimated to be equal in potency to thiouracil. Quantitative evaluation of certain goitrogens by McGinty *et al.* (2) based on the capacity of these substances to inhibit collection of radioiodine following single injections into rats, indicated that benzylthiouracil and propylthiouracil were approximately 10 times as active as thiouracil and methylthiouracil. These studies appeared to be quite consistent with those in which comparative potency was established by the chronic feeding tests. However, similar studies using chicks instead of rats showed that benzylthiouracil was considerably more active than propylthiouracil or thiouracil, the latter two possessing about equal inhibitory effects on uptake of radioiodine by the chick thyroid. Methylthiouracil was not included in the chick studies.

With the above observations in mind and because of the favorable position of benzylthiouracil in comparative toxicity studies in mice and rats, and its low solubility (see Fig. 1), the antithyroid effect of benzylthiouracil was investigated in hyperthyroid patients. Limited observations showed, however, that this compound was quite ineffective in lowering the basal metabolic rate in doses of 300 mg. daily, the same subjects responding subsequently to propylthiouracil treatment.

Speculation as to mechanisms involved in the failure of benzylthiouracil to control hyperthyroidism in man led to comparative urinary excretion

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studies in rats receiving single oral doses of 100 mg. of thiouracil and of the benzyl–, propyl- and methyl-derivatives. It was found that much less propyl- and benzylthiouracil was eliminated in twenty-four hours than thiouracil and methylthiouracil. In the case of benzylthiouracil, slightly increased recoveries were obtained following acid hydrolysis of the urine. This communication deals primarily with similar studies in man.

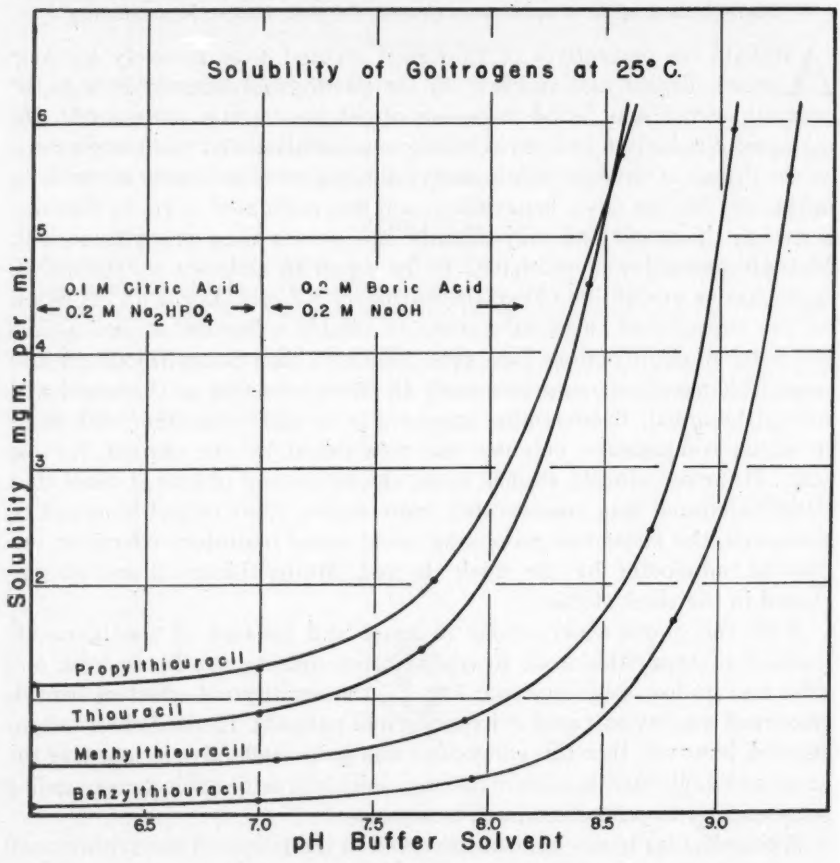


FIG. 1

## METHODS

Adult rats were given 100 mg. of the drug in 0.4 ml. 10 per cent acacia solution by stomach tube and placed, two in a cage, over glass funnels. Total 24-hour urine was collected. In the studies in man, two normal subjects, after morning voiding of urine, were given capsules containing 500 mg. of the drug approximately one-half hour before breakfast. Blood sam-

ples were drawn at two and one-half, five, and nine hours following administration of the drug. Urines were collected at irregular intervals over twenty-four hours, an aliquot of each collection being analyzed separately. The daily routine of meals was not altered.

The method of determining thiouracil and thiouracil derivatives in urine is modified from a procedure described by Grote (3) for use with organic compounds containing C–SH, C–S–S–C, and C=S groups. The reagent is prepared by treating sodium nitroprusside solution with hydroxylamine, sodium bicarbonate and bromine. The exact nature of the reaction with the sulfur-containing groups is not known, but it appears to be sensitive and gives quantitative results with thiouracil and its carbon 6-substituted derivatives.

## Reagents

1. *Stock solution of Grote's reagent:* Dissolve 0.5 Gm. sodium nitroprusside in 10 ml. of water and add 0.5 Gm. hydroxylamine hydrochloride. Mix for 2 minutes. Then add 1 Gm. sodium bicarbonate and mix for 5 minutes. Add 0.1 ml. bromine and filter into a 25 ml. flask and dilute to volume. This stock solution is relatively stable for months if kept in a refrigerator.
2. *1 per cent hydroxylamine hydrochloride in water.*
3. *Buffer—pH 7.0:* 35.3 ml. of 0.1 M citric acid is added to 164.7 ml. of 0.2 M disodium phosphate. Adjust to pH 7.0 with a Beckman pH meter.
4. *Thiouracil or thiouracil derivatives standard of 100 mg./L. in water.*

## Procedure

*Preparation of modified reagent:* Excess bromine in the stock solution of Grote's reagent is eliminated by addition of a measured amount of hydroxylamine. However, excess hydroxylamine interferes with the sensitivity of the color reaction with thiouracil. Therefore the optimum amount of hydroxylamine to produce the maximum color development in minimum time is found by experiment and added to the stock Grote's solution. The following procedure is used:

To 2 ml. portions of Grote's stock reagent add .05, .10, and .15 ml. of the hydroxylamine solution. Then to mixtures of 2 ml. buffer, 1 ml. thiouracil standard and 2 ml. water, add 0.3 ml. of hydroxylamine-treated Grote's reagent. The rate of color development is followed by periodic readings in the Coleman Jr. spectrophotometer set at 680 mμ. The concentration of hydroxylamine which produces maximum color in minimum time is used to prepare the modified reagent used on biologic fluids. Modified reagent should be freshly prepared.

### *Urine*

All urine samples were diluted to a volume in milliliters equal to the collection period in hours multiplied by 200. The concentration of thiouracil or thiouracil derivative in urine was determined by mixing 2 ml. diluted urine with 2 ml. water and 2 ml. of buffer and then adding 0.3 ml. modified Grote's reagent. The solutions were mixed thoroughly and read in the spectrophotometer after 5 minutes standing. The amount of thiouracil or thiouracil derivative present was estimated in all cases by comparing the color intensity developed in unknown urine to the increased color intensity of the same urine to

which known amounts of corresponding thiouracil derivative had been added. Blank corrections may be avoided by setting the optical density reading at zero with diluted urine obtained from the same subject prior to treatment with drug and preferably over a corresponding time interval.

Milligrams of thiouracil or thiouracil derivative excreted in a urinary collection interval is calculated from the equation, $\frac{A \times C \times D \times 100}{B - A}$ where A is equal to the optical density of the unknown diluted urine, B is equal to the optical density of the unknown diluted urine to which is added a known amount of thiouracil or thiouracil derivative standard, C is equal to amount of thiouracil in milligrams added in B, and D is equal to the collection interval in hours.

With certain urine samples it was found that acid hydrolysis produced an increase in color intensity with Grote's reagent. Particularly was this the case with urine from human subjects who were given propyl- and benzylthiouracil and was thought to be due to the presence of a conjugated ı onreactive form of the drug. In such cases, acid hydrolysis was carried out as a necessary part of the procedure for determination of these compounds. The following method was used: In a calibrated tube add 2 ml. of diluted urine, 1 ml. of $H_2O$, and 0.25 ml. of 12 N HCl. Mix and heat on a steam bath for 10 minutes. Cool to room temperature and add one drop 1 per cent phenolphthalein. Make basic with NaOH, and then neutralize exactly to the disappearance of color. Dilute to 6 ml. volume with buffer. Then add 0.3 ml. of modified Grote's reagent and mix. Read in a spectrophotometer after 5 minutes, setting the urine blank to zero optical density. The amount of thiouracil or thiouracil derivative is then estimated as above.

### *Plasma*

To 2 ml. plasma add 1 ml. $H_2O$, 2 ml. 10 per cent sodium tungstate and 4 ml. 0.33 N $H_2SO_4$. Mix and centrifuge after one-half hour. To 3 ml. of the supernatant add 1 drop normal NaOH (to neutralize to approximately pH 7.0), 2 ml. buffer and 0.3 ml. modified Grote's reagent. Mix well and read in the spectrophotometer after 5 minutes. A plasma standard is prepared by adding to 2 ml. of normal plasma 0.5 ml. thiouracil (or thiouracil derivative) standard, 0.5 ml. $H_2O$, .2 ml. 10 per cent $Na_2WO_4$ and 4 ml. 0.33 N $H_2SO_4$ and proceeding as above. A similarly prepared plasma blank using normal plasma without added thiouracil standard is set at zero optical density. Micrograms per milliliter of plasma sample is calculated from the ratio of optical densities of the plasma unknown to the plasma standard, multiplied by 25.

## RESULTS

Data from rat studies are shown in Table 1. The observations indicate first, that substantial proportions of the ingested doses of thiouracil and of methylthiouracil are excreted in twenty-four hours in contrast to the low values obtained in the cases of propyl- and benzylthiouracil. That these low values are not due to failure of intestinal absorption was indicated, at least in the case of benzylthiouracil, by a recovery of only 2 per cent of the ingested dose in 24-hour fecal collections. Secondly, urines from rats given thiouracil, methylthiouracil and propylthiouracil show little change after acid hydrolysis whereas similar treatment of urines from rats given ben-

TABLE 1

| Compound administered (100 mg.) | Per cent recovery of drug in 24-hour urine | |
|---|---|---|
| | Unhydrolyzed | Hydrolyzed |
| Thiouracil | 30 | 21.5 |
| Methylthiouracil | 38 | 35.0 |
| Propylthiouracil | 5 | 6.5 |
| Benzylthiouracil | 4 | 12.0 |

zylthiouracil causes them to show a moderately but definitely increased concentration of drug in the hydrolyzed urine.

Similar studies in dogs given single doses of 300 mg. thiouracil, methylthiouracil, propylthiouracil and benzylthiouracil respectively yielded no information from urine analyses because of high concentrations of interfering chromogenic substances. However, drug concentration values in the plasma showed that more rapid absorption of thiouracil and methylthiouracil occurred than of propyl- or benzylthiouracil. Plasma concentration curves are shown in Figure 2.

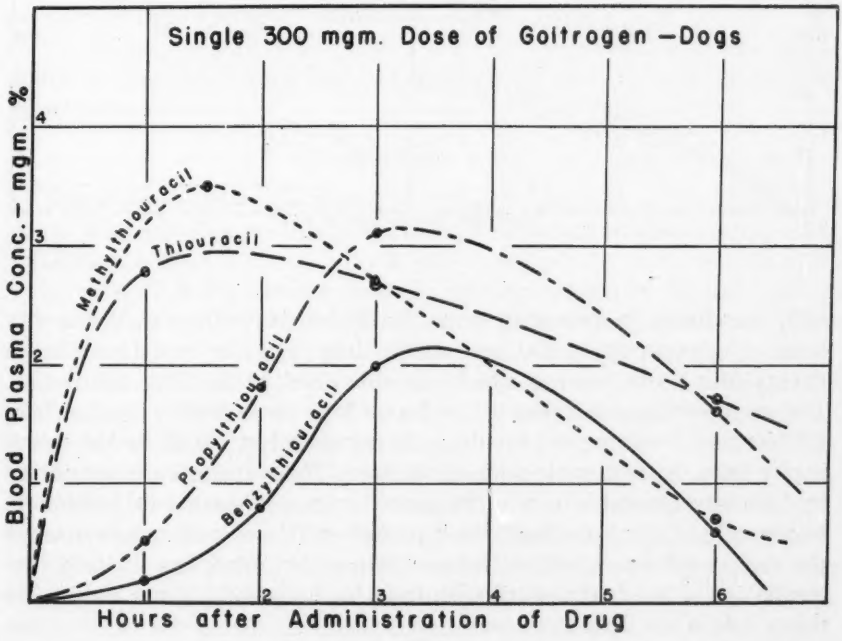


FIG. 2

Data from the studies in man carried out on two normal subjects are shown in Figure 3. It will be observed in the case of thiouracil and methylthiouracil that approximately 40 per cent of the ingested dose of 500 mg. is eliminated in twenty-four hours, excretion being rapid in the first four to six hours but continuing throughout the entire period. Hydrolysis of these urines did not materially alter the concentration of drug present.

In both subjects receiving benzylthiouracil, none of the compound as

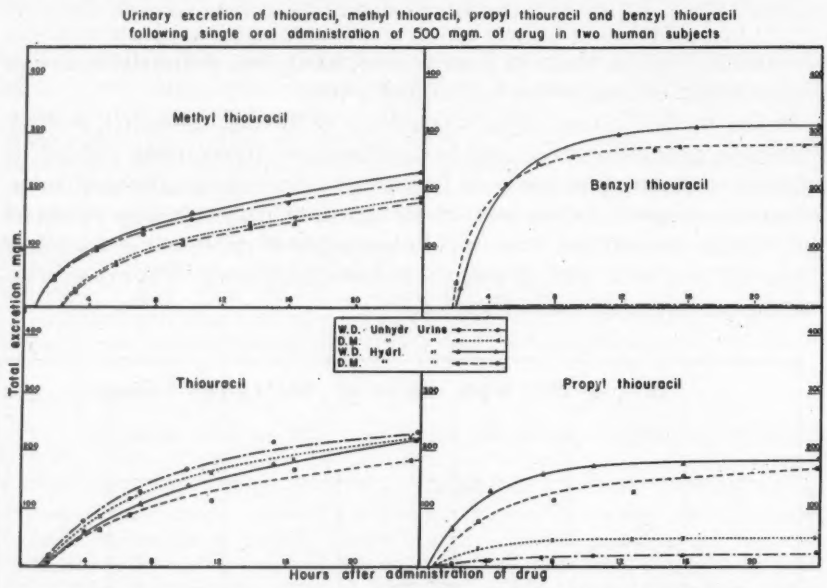
Urinary excretion of thiouracil, methyl thiouracil, propyl thiouracil and benzyl thiouracil following single oral administration of 500 mgm. of drug in two human subjects
Methyl thiouracil
Benzyl thiouracil
Thiouracil
Propyl thiouracil
W.D. Unhydr Urine
D.M. "
W.D. Hydrl. "
D.M. "
Total excretion - mgm.
Hours after administration of drug

FIG. 3

such, was found in untreated urine. On hydrolysis with acid, however, a total of approximately 300 mg. of the drug could be accounted for in twenty-four hours, most of which was eliminated in the first eight hours. The most obvious conclusion to be drawn from these findings is that benzylthiouracil is conjugated on absorption and rapidly eliminated in a conjugate form, hydrolyzable with dilute acid. This conclusion is supported by failure to recover any benzylthiouracil from a 48-hour fecal collection, in one subject, by a method which permitted 92 per cent recovery when the compound was mixed with feces. It may be noted here that *in vitro* incubation of benzylthiouracil with feces for forty-eight hours resulted in minor loss of the drug.

It appears that propylthiouracil, like benzylthiouracil, is conjugated although to a lesser extent than in the case of the latter compound, 4 per cent of the ingested drug being excreted in twenty-four hours in one subject and 10 per cent in the other. Similarly, as in the case of benzylthiouracil, hydrolysis of urine led to release of the drug from its conjugate form. Analysis of hydrolyzed urine showed an average of 35 per cent recovery of the ingested dose of the drug in twenty-four hours, the bulk of the compound being excreted in the first eight hours after administration.

While one is not justified in assuming that comparative potencies of the antithyroid drugs as evaluated in animals can be applied to man, the relatively low activity of propylthiouracil and complete ineffectiveness of benzylthiouracil were difficult to explain. The above observations, however, may serve to account for the discrepancies between findings in animals and clinical results with these two drugs. It may be mentioned in this connection that Stanley and Astwood (4) have shown that propylthiouracil in man is somewhat less active than thiouracil as judged by its ability to inhibit uptake of tracer doses of radioactive iodine.

Analytical results from determinations of these compounds in blood did not reveal information of major importance except to indicate that thiouracil and methylthiouracil remained in the blood for longer periods and at slightly higher concentrations than did propylthiouracil.

Preliminary attempts at purification and identification of the conjugates of propylthiouracil and benzylthiouracil gave no clue as to their properties.

## SUMMARY

Thiouracil, 6-methylthiouracil, 6-n-propylthiouracil and 6-benzylthiouracil were administered orally to two normal human subjects in single 500 milligram doses.

Urinary excretion studies showed that approximately 40 per cent of thiouracil and methylthiouracil are excreted in twenty-four hours. Not more than 10 per cent of propylthiouracil and none of the ingested dose of benzylthiouracil, as the free compounds, are excreted in the same period. Following acid hydrolysis of these urines, 35 per cent and 60 per cent respectively of these drugs were found.

The results indicate that benzylthiouracil and, to a lesser extent, propylthiouracil are conjugated on absorption and eliminated as an acid hydrolyzable complex of unknown nature. Complete conjugation of benzylthiouracil and partial conjugation of propylthiouracil may explain the complete inactivity of the former drug and the relatively poor activity of the latter compound in clinical hyperthyroidism.

## REFERENCES

1. Astwood, E. B.; Bissell, A., and Hughes, A. M.: Further studies on the chemical nature of compounds which inhibit the function of the thyroid gland, *Endocrinology* **37**: 456, 1945.
2. McGinty, D. A.; Rawson, R. W.; Fluharty, R. G.; Wilson, Mary; Riddell, Charlotte, and Yee, Hilda: The effect of certain goitrogenic drugs on the absorption of radioactive iodine by the thyroid gland, *J. Pharmacol. & Exper. Therap.* **93**: 246, 1948.
3. Grote, I. W.: A new color reaction for soluble organic sulphur compounds, *J. Biol. Chem.* **93**: 25–30, 1931.
4. Stanley, M. M., and Astwood, E. B.: Determination of the relative activities of antithyroid compounds in man using radioactive iodine, *Endocrinology* **41**: 66, 1947.

# METHYLTHIOURACIL IN THE TREATMENT OF HYPERTHYROIDISM*

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METHYLTHIOURACIL has proved to be highly effective in the control of hyperthyroidism. First reported at a meeting of the Danish Society of Internal Medicine on May 21, 1944 (1), many accounts of its use have been published since in Denmark, Sweden, England and Australia. The largest series of cases studied were those of Meulengracht, *et al.*(2,3), Magnusson and Soerensen(1), and Frisk(4). One article on the Danish work has appeared in the American literature (5).

Danish reports indicated that the drug retained its high efficacy when the doses were decreased from the huge amounts originally prescribed to quantities approximating those effective for propylthiouracil. This evidence suggested that a dose of methylthiouracil might be established which would be as small as that of propylthiouracil and, at the same time, more effective.

In December, 1946, after having used propylthiouracil in the treatment of more than 300 patients with hyperthyroidism we wished to compare this experience with that obtained in the use of methylthiouracil. In the majority of patients propylthiouracil had been effective in doses of 200 to 300 mg. per day. For comparison, similar doses of methylthiouracil were given. Up to April 15, 1948, 100 patients with hyperthyroidism have been treated with methylthiouracil.

### *Selection of cases.*

Patients chosen for treatment with methylthiouracil are classified in the following groups:

1) Those who are unsuitable for surgery because of poor cardiovascular status, frequently due to severe arteriosclerotic or hypertensive heart disease, or both; patients who have had previous thyroid operations; and psychotic patients.

2) Those in whom surgical risk can be largely eliminated by complete preoperative control of hyperthyroidism.

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3) Those who do not have a large goiter and in whom a medical cure seems feasible.

4) Those who refuse surgery.

In our practice methylthiouracil therapy is considered unnecessary as preoperative treatment in young persons with mild or moderate hyperthyroidism for the reason that it is time-consuming and does not appear to reduce the surgical risk. Prolonged treatment is contraindicated in any patient suspected of having carcinoma of the thyroid or substernal goiter. It is never recommended in the treatment of thyroid crisis because of its retarded action, and it is withheld from unintelligent and uncooperative patients.

## METHOD OF TREATMENT

The diagnosis of hyperthyroidism is established on clinical grounds. A basal metabolism test, leukocyte count, blood sugar determination, Wassermann test, and urinalysis are made. Recently, in a search for a better method of differential diagnosis, we have given a tracer dose of radioactive iodine when the diagnosis is in doubt.

Patients are not hospitalized except those who are verging on crisis, those who are extremely weak because of hyperthyroidism, and those who have severe complications.

The initial dose of methylthiouracil has been 200 or 300 mg. per day in divided doses usually given at meal time and at bed time. The smaller dose is given to patients with small goiters. In 5 instances the dose has been raised to 400 mg. per day when the response to lower doses was considered slow; in 1 patient it has been raised to 450 mg. In the future we intend to prescribe an initial dose of 400 mg. per day in patients with large goiters and severe hyperthyroidism.

The maintenance dose of the drug now used is approximately the same as the initial dose in almost all instances. Formerly the dose was lowered substantially as soon as the hyperthyroidism was brought completely under control. This was because of fear of toxic reactions. Recently we have discontinued this practice because: 1) a dose lower than that needed for the initial control sometimes resulted in an exacerbation of the disease and 2) the maintenance of some degree of hypothyroidism during treatment appears to increase the chances of a lasting remission. This is supported by the observation that patients with postoperative hypothyroidism lasting for months are less likely to develop recurrences than those not showing signs of myxedema after surgical treatment. On the other hand the natural history of hyperthyroidism is such that the possibility of spontaneous remission unrelated to the hypothyroidism cannot be eliminated.

For these reasons the dose of methylthiouracil is not reduced below 200 mg. per day. If myxedema supervenes during the course of treatment, ½ to 2 gr. of desiccated thyroid per day is given.

We give 10 to 20 mg. of iodine per day with methylthiouracil to all patients. It has been shown that iodine in this amount does not decrease the effectiveness of propylthiouracil(6). Hence iodine is used in the attempt to prevent increased vascularity of the thyroid.

Diets supplying up to 4000 calories a day are recommended when necessary to prevent loss or to produce gain in weight. Sedation is prescribed when necessary to overcome excessive restlessness until hyperthyroidism is under control, and vitamins are occasionally supplemented. Cardiovascular disease, diabetes, or other complicating disorders are treated as indicated.

Patients are asked to return for re-examination once each month or twice each of the first few months, and later at two-month to three-month intervals. They are advised to report any untoward symptoms at once and are warned that a blood count is imperative at the first indication of sore throat or fever. It is not necessary to take frequent leukocyte counts; those made on our patients have been for investigative purposes. Measurements of the eyes have been made with a Hertel's exophthalmometer in 41 patients. In only a few have repeated measurements been made thus far.

## RESULTS

This report is based on the first 100 patients given methylthiouracil at the Cleveland Clinic. Some have been treated for less than two months; the longest, for sixteen months.

The cases have been divided into 6 groups:

1. *Hyperthyroidism completely controlled.* This group is composed of 41 patients, 34 of whom had diffuse thyroid enlargement and 7, nodular goiters. No attempt was made to estimate the size of the glands in grams. The diffuse goiters were all small or of moderate size. Nine were cases of postoperative recurrence. The nodular goiters were moderate or large in size. Two were extremely large, and one of these showed by far the slowest response to treatment. This patient was 72 years old. Patients in whom hyperthyroidism recurs after adequate medical therapy may be candidates for thyroidectomy. However, surgery is not advocated when a risk element exists, whether because of the age of the patient or for other reasons. A thiourea derivative or radioactive iodine may be employed satisfactorily in such cases.

2. *Hyperthyroidism not completely controlled under treatment.* Thirty patients are under treatment, their hyperthyroidism incompletely con-

trolled. In each of 18, only 1 examination and basal metabolic determination has been made. These patients are still under our care but have not been treated long enough for the data to serve as a basis for evaluation of the therapy. Twelve appear to be responding satisfactorily to treatment. Two of the 10 under care elsewhere are improving steadily, and 1 is symptom-free and has been working regularly after treatment with methylthiouracil for two months.

3. *Thyroidectomy* has been performed successfully to date on 7 of the 100 patients. In these cases operation was advised in preference to prolonged medical treatment for the following reasons:

One patient had a solitary adenoma. Four had moderately large nodular goiters, seemed poor prospects for medical treatment and presented good surgical risks. One of these is also included in group 1 because of a previous excellent response to methylthiouracil. In 2 of these carcinoma was suspected but not found. One patient had an exacerbation of symptoms following reduction in the dosage of methylthiouracil which was recommended elsewhere. One had a large nodular goiter and was operated upon. Prompt control of the hyperthyroidism seemed especially desirable in this patient because of severe active rheumatoid arthritis. Response to medical treatment had been slow.

4. *Change from proplythiouracil to methylthiouracil.* In 13 of our patients, treatment was changed from propylthiouracil to methylthiouracil after many months of therapy. This was done chiefly to observe any differences in the effectiveness of the two drugs. Nine of these cases were well controlled, and the basal metabolic rates were $\pm 0$ per cent or lower, at the time of the change. One patient who could not be considered for operation because of poor cardiac condition had a recurrence of hyperthyroidism after eighteen months of good control with propylthiouracil. Two others had a relatively incomplete response since, although they were clinically well, the basal metabolic rates had never fallen below plus 10 per cent after thirty and forty-four weeks of treatment with propylthiouracil. Doses of 300 and 400 mg., respectively, had been administered for many weeks. Methylthiouracil was given to 1 patient because of several recurrences of rash and nausea after taking propylthiouracil.

5. *Remissions.* Little can be said concerning remissions after withdrawal of methylthiouracil because the treatment is now being continued for eight months or more in order to maintain complete control with subzero basal metabolic rates. Treatment has been discontinued in only 6 patients, after twelve, nine, nine, eight, six, and five months of complete control, respectively. Four remissions have continued for one, three, four, and four months, respectively. There have been recurrences in 2 instances, in one and four months respectively.

Poate (7) has reported remissions continuing after withdrawal of methylthiouracil in 57 of 63 patients for lengths of time varying from two to fifteen months. Remissions lasting less than a year have little significance.

6. *Poor responses.* In 11 patients the clinical results are considered poor. These "poor responses" are not due to ineffectiveness of methylthiouracil in controlling hyperthyroidism. Three patients refused to cooperate. The drug was either taken not at all or irregularly. In 1 patient the metabolic rate did not fall below plus 9 per cent during the administration of doses as high as 400 mg. per day for four months. The thyroid had enlarged considerably and operation was advised.

One woman, aged 64, remained ill in spite of a definite fall in basal metabolic rate. She also had hypertension and frequent attacks of angina pectoris. One woman, aged 62, was only slightly improved clinically. Her case was complicated by severe vascular disease and cerebral thrombosis. One patient discontinued treatment during an emotional upheaval and subsequent pneumonia. The disease is now well controlled. In one 68-year-old man with a large nodular goiter, Parkinson's disease and severe arterial hypertension, the basal metabolic rate fell to zero after thirty-five weeks of therapy. It is now controlled on 350 mg. per day. One 70-year-old woman died, having discontinued methylthiouracil a week before her last illness. The diagnosis in this case included adenomatous goiter with hyperthyroidism, arterial hypertension, auricular fibrillation, diabetes mellitus, cholelithiasis, and cataract. She had discontinued the use of insulin, and after a four-day illness with vomiting she died. We did not observe her in her last illness. A careful summary of the findings revealed the highest blood sugar level to be 138 mg. per cent, and a leukocyte count, 16,450 with 77 per cent granulocytes. Her death was ascribed to cardiac decompensation.

Two patients had neurocirculatory asthenia, which was the original diagnosis. Methylthiouracil was given as a therapeutic test but the drug failed to control either the metabolic rates, which varied from plus 5 to plus 28 per cent, or the associated symptoms. Lugol's solution given as a therapeutic test, also failed. These cases cannot be considered as instances of failure of methylthiouracil and, since the patients did not have hyperthyroidism, they are not included among the 100 who comprise the subject of this study.

### *Toxic effects*

Toxic effects have been recognized in 5 patients. In only one was treatment interrupted and iodine and thyroidectomy recommended. This patient was a 39-year-old woman who had a previous history of purpura hemorrhagica. She had developed a purpuric eruption while taking propylthiouracil in doses of 200 mg. per day. After having been treated for six months with methylthiouracil, blood studies revealed a leukocyte count

of 1450 with 9 per cent granulocytes, and there was an associated facial edema. There were no other symptoms. Several months later it was learned that no methylthiouracil had been taken for a period of two months prior to the discovery of the granulopenia. This, together with the known existence of a blood dyscrasia prior to methylthiouracil therapy, throws much doubt on the supposition that this was a toxic reaction due to the drug. Thyroidectomy was not performed. The hyperthyroidism was in complete remission six months after cessation of therapy. No abnormalities were found in the blood; bleeding and clotting time, platelets, and clot retraction were normal. The leukocyte count was 4500 with 62 per cent granulocytes.

In the other 4 patients the toxic effects were mild and in none of these was treatment interrupted. Two developed mild maculopapular rashes and in 2 a few transient painless subcutaneous nodules appeared.

Blood counts have not been made frequently in our patients. An initial leukocyte count was made in all, and in 2 the count was 3850 before therapy. In 24 patients, repeated white blood counts were made at intervals extending over many months. The lowest counts were 3600 and 3350 with 66 per cent and 50 per cent granulocytes, respectively, found in the second month of treatment. In the first of these, the leukocyte count rose during continued treatment to 7300 with 74 per cent granulocytes in the sixth month. In the second, the count rose to 6400 with 58 per cent granulocytes in the eighth month. In the remainder no significant trend was seen, all total leukocyte and granulocyte counts varying within the normal range.

Toxic effects appear to bear a close relationship to the dose of the drug used. It is interesting that a perusal of the data relating to doses and toxic effects which Barfred (5) has presented, as well as information from our own studies, indicate that no toxic effects of any consequence have been reported by any author who has used doses of methylthiouracil of 750 mg. per day or less.

### *Exophthalmos*

At present we can report on the status of exophthalmos, by actual measurement, in only 9 patients during methylthiouracil therapy. In these patients measurements were made two or more times over intervals varying from two to sixteen months. Some increase was observed in the proptosis present in 7 of the 9; the greatest increase was 5 mm. (from 20 to 25 mm.) over a period of sixteen months in 1 patient; it remained stationary in 2 patients and decreased 1 mm. in another. The eye signs studied appear to be the same after methylthiouracil therapy as after thyroidectomy (8). The results are summarized in the following table:

TABLE 1. STATUS OF EXOPHTHALMOS DURING METHYLTHIOURACIL THERAPY

| Case | Antero-posterior measurements in millimeters | | | | | | | | Result |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 18*<br>18 | | | 20<br>20 | | | | | +2 |
| 2 | 17<br>16 | | | | 18<br>17 | | | | +1 |
| 3 | 20<br>20 | | | 19<br>19 | 19<br>19 | | | | −1 |
| 4 | 27<br>26 | | | | 28<br>27 | | | | +1 |
| 5 | 20<br>19 | | 21<br>20 | | | 21<br>20 | | | +1 |
| 6 | 21<br>23 | | 24<br>26 | | | | | | +3 |
| 7 | 22<br>20 | | | | | | 21<br>21 | | ±0 |
| 8 | 20<br>20 | | 23<br>23 | | 23<br>23 | 25<br>26 | 24<br>25 | 25<br>25 | +5 |
| 9 | 22<br>20 | | | | 24<br>22 | | 23<br>21 | 23<br>21 | +1 |
| Months | 0 | 1 | 2 | 3 | 4 | 6 | 12 | 16 | |

* O.D. above; O.S. below, in each case.

*Comparative effectiveness of methylthiouracil and propylthiouracil*

In making a comparison of the efficacy of methylthiouracil and propylthiouracil we have selected only patients with diffuse goiter. Treatment was continued in all patients until, during the daily administration of a single dose, the basal metabolic rate fell to zero. Since in many patients levels of dosage were varied, the number of cases available for this part of the study is small. Patients who had such complications as asthma, severe hypertension, or cardiac decompensation were excluded. The results are summarized in Table 2.

These figures indicate that methylthiouracil in doses of 200 and 300 mg. per day is somewhat more effective than propylthiouracil. The differ-

TABLE 2. COMPARATIVE RESPONSE TO METHYLTHIOURACIL AND PROPYLTHIOURACIL IN GRAVES' DISEASE

| | | | | |
|---|---|---|---|---|
| Methyl-thiouracil | Dose/day | | 200 mg. | 300 mg. |
| | No. of cases | | 18 | 7 |
| | Response: | mean | 4.5 | 6.1 |
| | fall of B.M.R.* | max. | 9.1 | 8.8 |
| | %/wk. | min. | 2.0 | 4.5 |
| Propyl-thiouracil | Dose/day | | 200 mg. | 300 mg. |
| | No. of cases | | 20 | 20 |
| | Response: | mean | 4.1 | 3.6 |
| | fall of B.M.R. | max. | 7.5 | 10.4 |
| | %/wk. | min. | 2.7 | 1.2 |

* The basal metabolic rate in all patients fell to, or below, ±0%.

ence is not great, however, and there is a wide variation in response. This is not surprising since the degree of hyperthyroidism and the mass of thyroid tissue vary greatly. More consistency might be shown in a larger series of cases.

## SUMMARY

1. Methylthiouracil has been used in the treatment of 100 patients with hyperthyroidism for from one to sixteen months.

2. In doses of 200 to 400 mg. per day methylthiouracil is an effective and safe antithyroid agent.

3. Methylthiouracil appears to be somewhat more effective than propylthiouracil.

4. In our patients 10 to 30 mg. of iodine per day has been used concurrently throughout treatment.

5. In an attempt to produce the maximum number of lasting remissions our present plan in the use of methylthiouracil is to maintain a relatively hypothyroid state for eight or more months. During this period if symptoms of hypothyroidism arise they are treated with desiccated thyroid.

## REFERENCES

1. MAGNUSSON, P., and SOERENSEN, G.: Treatment of hyperthyroidism with methylthiouracil, *Acta med. Scandinav.* **125**: 263–282, 1946.
2. MEULENGRACHT, E., and SCHMITH, K.: Treatment of thyrotoxicosis with methylthiouracil, *Acta med. Scandinav.* **122**: 294–314, 1945.
3. MEULENGRACHT, E.; KJERULF-JENSEN, K., and SCHMITH, K.: cited by Barfred, A. (5), *Nord. med.* **32**: 2800, 1946.

4. Frisk, R. A.: cited by Barfred, A. (5) *Nord. med.* **32**: 2707, 1946.
5. Barfred, A.: Methylthiouracil in treatment of thyrotoxicosis, *Am. J. M. Sc.* **214**: 349–362 (Oct.) 1947.
6. McCullagh, E. P.; Hibbs, R. E., and Schneider, R. W.: Propylthiouracil in treatment of hyperthyroidism, *Am. J. M. Sc.* **214**: 545–552 (Nov.) 1947.
7. Poate, H. R. G.: Control of thyreotoxicosis by methyl thiouracil, *M. J. Australia* **2**: 93–106 (July 26) 1947.
8. McCullagh, E. P.; Ruedemann, A. D., and Gardner, W. J.: Exophthalmos of Graves' disease following pituitary irradiation, orbital decompression and electrocautery to the pituitary gland, *Tr. Am. A. Study Goiter*, 1942–1946, pp. 15–32.

# PROLONGED METHYLTHIOURACIL TREATMENT IN THYROTOXICOSIS. RESULTS AFTER CESSATION OF THE TREATMENT

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THE immediate results of the prolonged treatment of thyrotoxicosis with methylthiouracil are now so well known from numerous reports, that on this occasion we shall deal mainly with the *late* results. We are naturally not yet in a position to appreciate them fully, since the treatment with antithyroid compounds was introduced clinically by Astwood (1) only in 1943, so that we have no more than three or four years' experience to go on. Nevertheless it may be expedient even at this early date to consider what has come to light.

From previously published reports, both those of others (1), (2), (3), (4), (5), (6) and our own (7), (8) it appears that after a certain period of treatment which, although very variable, usually seems to be about nine to twelve months, one can discontinue the small maintenance dose of the antithyroid substance without any great risk of a relapse, while at the same time there is a tendency for the goiter to disappear. In short, it would appear from these preliminary results as though a cure of the disease had taken place.

## *Clinical Material*

Our own last report was published eighteen months ago, and in order to bring our results up to date, from August to October 1947, we undertook a systematic *after-investigation* of all our patients.

The material now comprises 211 cases of thyrotoxicosis admitted to Medical Department B, Bispebjerg Hospital from the beginning of 1944 through October 1947 (Table 1). In addition there were about 15 patients who had not been admitted but had been treated by one of us as outpatients. The systematic after-investigation does not include these ambulatory cases. The reason why the number of patients is large is that at the time there was temporarily a considerable increase in the incidence of thyrotoxicosis; it began in 1941 and reached its maximum in 1943–44. This "epidemic" was described by Meulengracht (9) and by K. Iversen (10) in Denmark. It was observed also in Norway (11).

Eighty-nine per cent of all the cases were in females. Since the Depart-

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TABLE 1. CLINICAL MATERIAL, DEPT. B, BISPEBJERG HOSPITAL, 1944–1947 (OCT.).

| | No. of patients |
|---|---|
| Cases of thyrotoxicosis admitted to hospital (in addition there were 15 cases in the out-patient department) | 211 |
| Treated with methylthiouracil | 192 |
| Treated with propylthiouracil | 19 |
| Thyroidectomy on account of results of histologic examination of the gland | 2 |

ment has twice as many beds for females as for males, these figures do not indicate the actual sex distribution in the "epidemic." The youngest patient was 15 years of age, the oldest, 78. The age distribution can be seen from Figure 1.

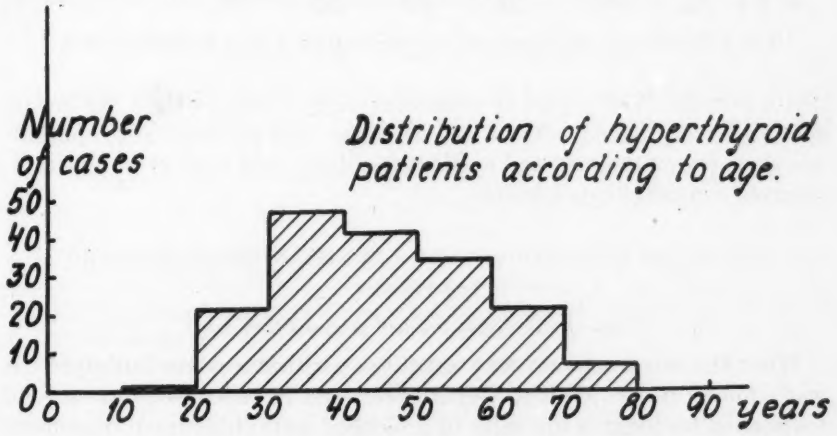


FIG. 1. Age distribution of patients with thyrotoxicosis in Medical Department B, Bispebjerg Hospital, 1944–1947 (Oct.).

The degree of severity of the cases was as follows:

| | | *Per cent of total* |
|---|---|---|
| Mild cases | (Basal metabolic rate up to plus 30 per cent) | 25 |
| Moderately severe cases | (Basal metabolic rate between plus 30 and plus 60 per cent) | 61 |
| Severe cases | (Basal metabolic rate over plus 60 per cent) | 14 |

Most (about 86 per cent) were cases of primary thyrotoxicosis. A previously existing nontoxic goiter could be detected in only 14 per cent of the cases; it was usually nodular. The majority of the cases were fairly recent. Thus most of the patients had had symptoms of thyrotoxicosis for less than one year (Fig. 2). In 13 cases there had been a relapse after an earlier

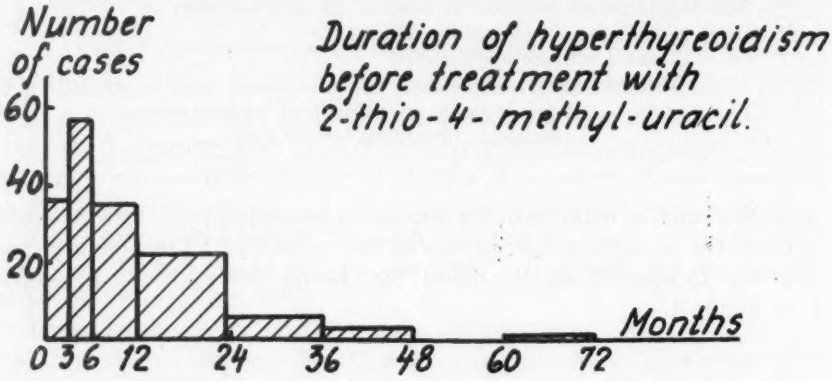


FIG. 2. Duration of thyrotoxicosis prior to treatment with methylthiouracil.

thyroidectomy. With regard to symptomatology—loss of weight, cutaneous and circulatory phenomena as well as goiter were predominant; ophthalmic signs (exophthalmos and eyelid retraction) were rare, or at any rate, occurred comparatively seldom.

## PROLONGED METHYLTHIOURACIL ADMINISTRATION AS STANDARD TREATMENT

### *Plan of investigation and preparation used*

When the new treatment with antithyroid substances was introduced, it was adopted in the Medical Department, and in order to obtain a solid foundation for judging the value of prolonged methylthiouracil treatment, the plan adhered to from the very outset was to treat *all* cases of thyrotoxicosis continuously, in an attempt to effect a cure. This procedure has since been strictly observed, with the proviso that at first a few patients were referred for thyroidectomy after preliminary methylthiouracil treatment, because it was of interest to observe the histologic picture of the gland influenced by the drug.

The preparation chosen was methylthiouracil (4-methyl-2-thiouracil). This was originally introduced in various places in Scandinavia as a substitute for the thiouracil recommended by Astwood and others. Methylthiouracil was easier and cheaper to produce and was clearly to be

regarded provisionally as the antithyroid substance best suited for the treatment of thyrotoxicosis.

When, later on, propylthiouracil (of which the antithyroid activity in rat experiments proved to be ten times greater than that of thiouracil) was introduced for therapeutic purposes, this preparation was used and 19 of our patients were treated continuously with it. In an earlier publication (12) we have given an account of our experiences with this preparation. Its antithyroid effect in thyrotoxicosis in man, however, was not nearly so great as one would have expected from the animal experiments, and therefore it can hardly have any great therapeutic value except that it could be employed in certain cases where methylthiouracil caused hypersensitivity reactions. The 19 patients treated with propylthiouracil are excluded from the present report.

The dosage of methylthiouracil was: 0.25 Gm. three times daily usually for two to three months. Following a drop in the basal metabolism and an increase in weight, the dose was reduced to 0.25 Gm. once or twice daily, usually for a few months. The final dose was small, namely, 0.125 Gm. daily or three times a week, usually for a number of months.

### *Patients whose treatment was interrupted*

In some patients the treatment was stopped or they themselves terminated it for various reasons (Table 2). Thus 5 were transferred for removal

TABLE 2. CHANGED TO SURGICAL TREATMENT FOR VARIOUS REASONS

| | No. of patients |
|---|---|
| Thyroidectomy: control could not be achieved because of patients' lack of cooperation | 2 |
| Thyroidectomy at patients' request (cosmetic reasons) | 3 |
| Thyroidectomy because of compression of the trachea | 2 |
| Total | 7 |

of the goiter because from impatience, or indifference and lack of understanding, they could not exercise the requisite control; or for cosmetic reasons they wished to get rid of the goiter.

Two patients were transferred for thyroidectomy on account of symptoms of tracheal compression. In one case there was a retrosternal goiter which had not previously given rise to any troublesome compression of the trachea but, as the gland enlarged temporarily during the treatment, signs of compression developed and it was necessary to terminate the treatment

and refer the patient for removal of the goiter. In another patient with retrosternal goiter the treatment was carried through without difficulty.

Another kind of therapy was resorted to in the case of 13 patients on account of symptoms of hypersensitivity (Table 3). The hypersensitiveness revealed itself with a drug eruption, fever, conjunctivitis, headache and pains in the extremities. These symptoms occurred either singly or associated in different ways. Agranulocytosis was met with in only one case. It was benign in character and the patient recovered quickly on discontinuing the methylthiouracil and being given a blood transfusion and

TABLE 3. CHANGED TO OTHER TREATMENT ON ACCOUNT OF *hypersensitiveness* TO METHYLTHIOURACIL

| | No. of patients |
|---|---|
| Thyroidectomy | 5 |
| Continued with propylthiouracil; tolerated | 5 |
| Continued with propylthiouracil; not tolerated: continued with iodine; tolerated | 2 |
| All treatment discontinued | 1 |
| Total | 13 |

penicillin by injections. We have previously discussed these hypersensitivity symptoms more fully.

*Patients who completed the treatment*

There remained 170 patients in whom the course of the treatment could be completed.

The *duration of the treatment* was, as a rule, twelve months. This indicates that the dose the patients received was fairly soon reduced to a small maintenance dose which was kept unchanged for several months. As time went on we were inclined to extend this last phase. The period of treatment for those considered to have completed the course varied from five to thirty-seven months (Fig. 3).

The treatment was begun in the hospital and continued after the patient had been made an out-patient under supervision. The *duration of the stay in the hospital* varied with the nature of the case. The varying periods are shown in Fig. 4. Gradually it became our conviction that residence in the hospital could be curtailed, and that a number of the patients could be treated entirely as outpatients, provided they were under regular supervision by one or more doctors who were familiar with the treatment.

When the patients were discharged from the hospital and passed over to

ambulant treatment they were usually able to *resume their work* immediately or soon afterwards. Fifty per cent of those undergoing prolonged treatment could return to work immediately after discharge from the hospital wards, *i.e.*, about one month after the treatment was started. Twenty-

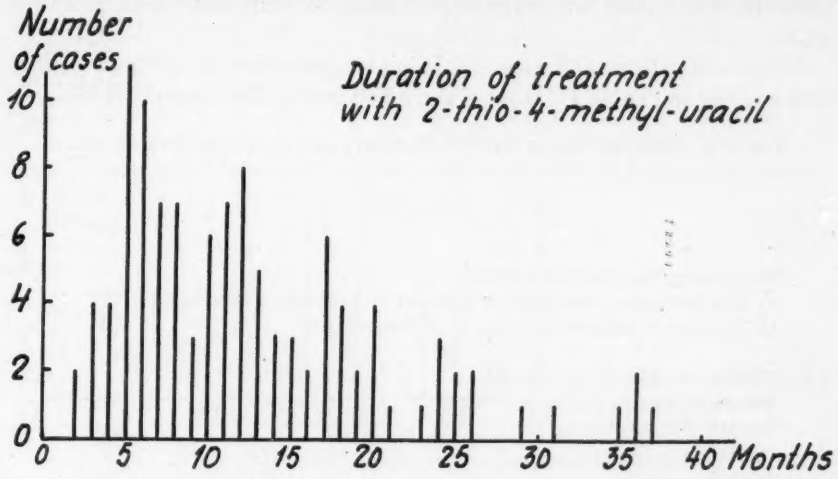


FIG. 3. Duration of treatment with methylthiouracil in patients with thyrotoxicosis in whom the course of treatment was completed.

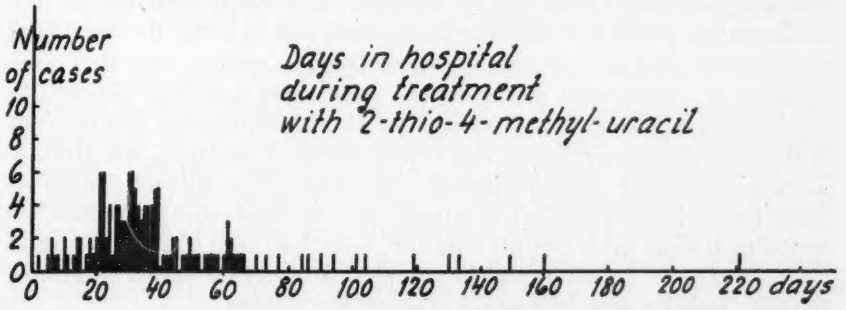


FIG. 4. Length of residence in hospital during treatment of thyrotoxicosis with methylthiouracil.

nine per cent were not able to work until two to four months, on an average, after discharge. Two per cent stated that they were not fit for work on account of the thyrotoxicosis, even after thorough treatment, although there were no visible objective grounds for this attitude. Eleven per cent did not work on account of their age or another nonthyrotoxic disease. We have in fact been more and more inclined to direct patients to work

earlier. When once the most prominent thyrotoxic symptoms have vanished, the patients will usually be able to work during the rest of the treatment, if not prevented by age or a complicating disease. In judging the value of the treatment it is important to realize that prolonged or continuous treatment does not indicate prolonged or continuous incapacity for work.

Of the 170 patients, 38 were still being treated when the after-investigation was begun (Table 4). Most of these had been under treatment for com-

TABLE 4. DISTRIBUTION OF THE 170 PATIENTS AT THE AFTER-INVESTIGATION

| | | No. of patients |
|---|---|---|
| 1. Still undergoing treatment as follows: | | 38 |
| a) Uninterrupted treatment or resumed on account of false relapse | 28 | |
| b) Treatment resumed on account of true relapse | 10 | |
| 2. Treatment omitted, as follows: | | 132 |
| For more than 3 months | 101 | |
| For less than 3 months | 20 | |
| Could not be traced | 7 | |
| Died from other causes | 4 | |

paratively so short a time that no attempt was made to interrupt it. In a small number we tried to stop the medication, that is to say the small final maintenance dose, but the symptoms returned so quickly that they were regarded as a persistence of the disease rather than a genuine relapse. By a quick flare-up we mean one occurring within three months. Ten per cent of the cases were *true* relapses, and a fresh course of treatment was started. As true relapses we have considered cases in which the patient had previously finished treatment but in whom, after an intervening symptomless period of at least three months' duration, there had been a return of thyrotoxic symptoms. In our cases the symptom-free period varied from nine to thirty months, with an average of seventeen months.

Amongst those who had had a quick flare-up of symptoms (spurious relapse) after a trial withholding of the drug, there were some, 2 in particular, in whom we had tried unsuccessfully time after time to discontinue treatment. It is obviously a question here of cases of a chronic nature in which the patients need very long or perpetual treatment in spite of the fact that they seem well and feel fit while it is in progress. One of these patients had previously had thyroidectomy performed twice followed by a relapse each time.

There remained 132 patients who, at the time of the after-investigation,

had completed their treatment. Of these, 20 had not yet reached the three-month limit after the end of treatment. One hundred and one had been without treatment for over three months. The observation period after the termination of treatment in this group varied from three to thirty-four months with an average of seventeen months (Fig. 5). The addresses

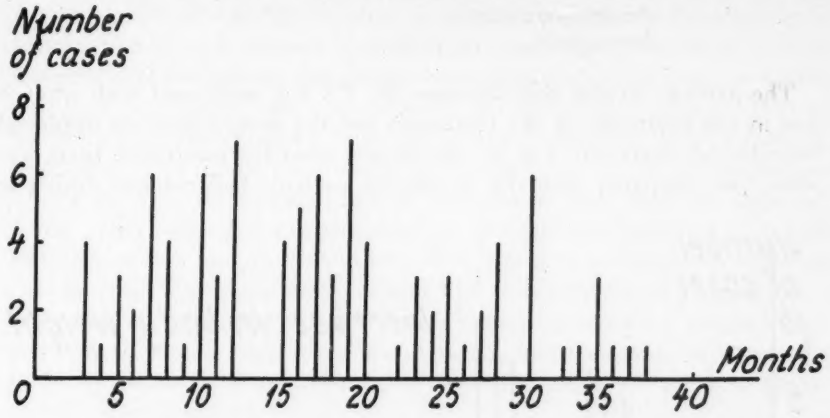


FIG. 5. Time that elapsed between the termination of methylthiouracil treatment and the after-investigation.

of 7 were unknown and we were unable to get into communication with them. Four had died of causes other than thyrotoxicosis.

*Condition of patient after termination of treatment*

The immediate effect of methylthiouracil on the general thyrotoxic symptoms such as the loss of weight, high basal metabolism, cardiac and ocular disorders, has been described previously (7) by us, and is now so well known generally that on this occasion, when attention is being concentrated on the late results, we shall pass over that phase of the subject.

The estimate of the condition *after* the treatment is based on the after-investigation of the 170 patients mentioned, especially 101 of them who had been without treatment for more than three months. At the after-investigation the following clinically detectable thyrotoxic symptoms were noted: loss of weight and in most cases, an increase in basal metabolism and the size of the goiter.

In the 101 patients who had stopped taking methylthiouracil for more than three months and who showed no signs of relapse, except for the goiter in some cases, very few symptoms were found which might have a connection with the earlier thyrotoxic condition. These residual symptoms were as follows:

| | *No. of cases* |
|---|---|
| Abnormally hot skin | 1 |
| Hand tremor | 1 |
| Eyelid retraction | 4 |
| Edema of eyelid | 1 |
| Exophthalmos after thyroidectomy | 1 |
| Perpetual arrhythmia | 1 |
| Nervousness | 2 |

The average weight was increased by 7.3 Kg. compared with what it was at the beginning of the treatment but the weight increase displayed considerable variation (Fig. 6). Sometimes, after the treatment, there was some loss compared with the weight the patients had reached during or

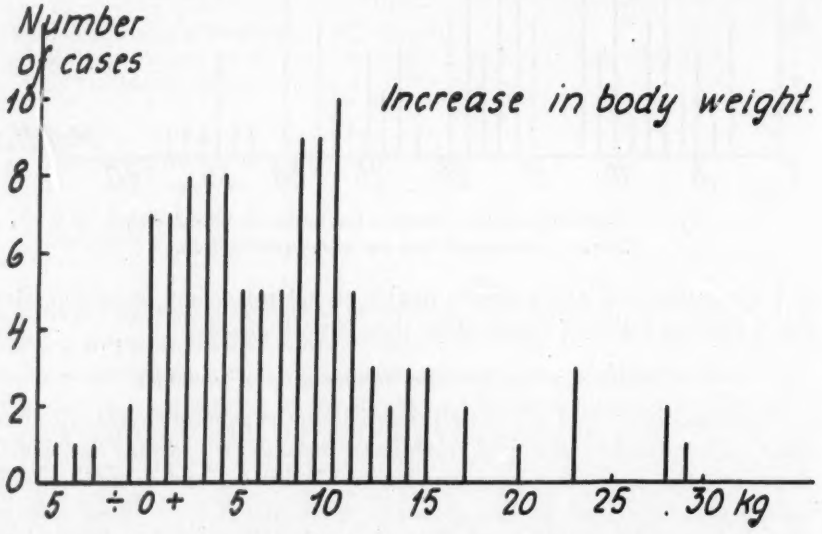


FIG. 6. Final increase in body weight at the after-investigation at different times after the completion of methylthiouracil treatment for thyrotoxicosis.

just after the treatment. Some patients had put on so much weight (as much as 30 to 35 Kg.) during the treatment that a certain loss later was only to be expected and was often deliberately aimed at. It would seem as though the patients ended up with the body weight which was "natural" for the individual concerned.

The basal metabolism was determined in the after-investigation in most cases and in all cases in which the residual symptoms or loss in weight aroused suspicion of a relapse; but we did not feel it necessary to check the clinical impression by a metabolism determination in any large number of

instances. It is now our opinion that a metabolism determination in an after-investigation of ambulant patients such as we have undertaken, is of limited value and is often inferior to the clinical observation, provided the latter is the opinion of persons who are versed in the investigation and control of thyrotoxic patients. Exactly the same view has recently been put forward by Wahlberg (13). In order to be fairly reliable the metabolism determination in an *ambulatory* patient presupposes very favorable and stable experimental conditions; and, at all events with us, it has proved very difficult to provide such conditions. Time after time it has happened that we have obtained an increased value which was at variance with the clinical impression, and a repetition of the determination a day or two later gave a different result that was more in accordance with what we expected. Quite apart from the impracticability of routine repeated metabolism estimations in a long-continued after-investigation, we therefore maintain that its reliability is not very evident, and that a practised investigator—indeed often the patient himself—is just as capable of telling whether there is a relapse or not. Among the 101 patients, however, none of those who had had metabolism tests showed a value above plus 20 per cent on repeated determinations.

The state of the *goiter* was investigated with particular interest. As is known, the goiter persists while the treatment is in progress; moreover a diffuse increase in size sometimes occurs as a transitory phenomenon some time after the commencement of the treatment, especially when the latter reduces the metabolism below the normal level. This is an overdose effect, which disappears as soon as the dose of the drug is regulated. But irrespective of a possible temporary increase in size, the goiter persists during treatment. The problem to be solved by an after-investigation is whether the goiter will disappear after the course of treatment is over, a point which our earlier investigations indicated (7). As previously pointed out (8), it is a difficult matter to estimate the size of the goiter by any trustworthy method. The circumference of the neck is of very little help because there is another tissue which varies simultaneously, namely the subcutaneous fat of the neck, which increases with the weight. Some workers, Means in Boston for example (personal communication), believe that by palpating the goiter they can compute the weight of the gland in grams, roughly of course, but nevertheless approximately. Our methods were the written description of the goiter and the illustration of the goiter by means of a diagram (8). We prefer the latter method. With these two methods we have obtained the following results:

The after-investigation of the 20 patients in whom the treatment had ended less than three months before, together with the 101 in whom it had ceased for more than three months, showed that 50 per cent had no goiter;

29 per cent because there had never been any, and 21 per cent because it had disappeared. Fifty per cent still had goiter at the after-investigation; in 24 per cent it was smaller than originally, and in 26 per cent it was unchanged. Two patients who had both been observed less than three months, had a larger goiter than when the treatment was commenced.

It can therefore be asserted that in most cases, after the treatment is concluded, the goiter gradually diminishes in size and in a few cases it disappears entirely. The goiters most likely to persist are the nodular ones which have frequently been in existence before thyrotoxicosis supervenes. Nevertheless we consider we have demonstrated the theoretically interesting fact that nodular goiter also undergoes a decrease in size after the treatment, compared with what it was at the beginning.

### *Number of relapses*

As mentioned, there were 10 patients among those undergoing after-investigations who developed what we regarded as genuine relapses. After courses of varying duration they were considered to have completed their treatment, and the drug was discontinued. But following a lengthy and entirely symptomless period, thyrotoxic symptoms began to appear again, and the patients were started on a fresh course of treatment. The symptomless periods varied from nine to thirty months. The number 10 should be compared with the number 111 which comprises all those who had had the drug for more than three months.

Thus for the present the relapse frequency may be put at about 9 per cent. This is a high value, for the presence of even mild thyrotoxic symptoms caused the case to be classified as a relapse. Some of the relapses therefore were doubtful and the rest were mild; but we preferred to renew the treatment without delay rather than wait until the relapse had become well established. On the other hand, the observation period was brief, and one must expect several relapses to make their appearance gradually in the course of years, just as one witnesses late, or even very late, relapses after subtotal thyroidectomy. We cannot yet predict which patients are liable to get relapses.

## DISCUSSION

### *Choice of treatment*

As stated, the continuous treatment was planned by us on a definite experimental basis, to be carried out in *all* the thyrotoxic patients who came to the Department.

In this investigation it was found that some of the patients (Tables 2 and 3) stopped the treatment, or the latter had to be interrupted for some

reason or another during its course. But the investigation has also proved that apart from these accidents all thyrotoxic patients can be treated according to this principle and good results obtained.

Whether, then, in the individual case or as standard treatment one will choose the conservative medical treatment or the operative—that is, subtotal thyroidectomy after preoperative preparation with iodine—depends on a number of factors which we have previously discussed (7) and which can be perceived more clearly now, although we are not yet in a position to form a final opinion.

With the operative treatment the mortality varies with the time and place. Keeping to the Danish figures we may recall that Sørensen (14) in 1945 estimated the mean operation mortality for a prior 10-year period for Danish hospitals at 2.7 per cent. In special departments the operation mortality is lower. Thus Bertelsen and Christensen (15) in 1947 found, for a previous 5-year period in the Dahl-Iversen Department of the University Hospital in Copenhagen, a mortality as low as 0.7 per cent, and in operations for relapses, 2.6 per cent. In contrast to these figures there are the extensive American collective statistics (16) which show a mortality of 0.5 per cent from agranulocytosis during continuous treatment with thiouracil compounds. This figure, however, relates to the early stage of the treatment before observers were familiar with the complications and their treatment, so that presumably it must be lower now.

A comparison of the non-fatal sequelae of subtotal thyroidectomy (such as recurrent-nerve paralysis and postoperative tetany) with the toxic reactions (such as drug fever, rash and headache) which may be encountered during continuous treatment with thiouracil compounds is, in our opinion, in favor of the methylthiouracil treatment (compare earlier publications).

The dislike of having to be operated upon has to be pitted against the dislike and inconvenience of long-continued control. We believe that the latter can be rendered more tolerable by restricting the number of determinations of the basal metabolism in favor of the clinical investigation of the routine investigator, and that the blood examination can be dispensed with in favor of an immediate report to the doctor at the first sign of any complications arising. We have previously stressed that this system must be regarded as the safer method, but it is clear that geographical conditions may here play a decisive role: if the patients live in the vicinity of the hospital it is easy to carry out the supervision, but if they are spread over a wider area, is it more difficult.

We think that the cosmetic question will in great measure decide the future distribution of patients between the two forms of treatment. It is a fact that a scar on the neck is a matter of consequence to many patients.

Nobody is bold enough to guarantee a faultless cicatrix beforehand, nor can it be denied that union of the skin to the deeper tissues is disfiguring, especially when attended by retraction. For young women with a diffuse goiter it is a consideration which the doctor also ought to take into account in giving advice. It is a different matter in the case of nodular goiter, which apparently has not the same tendency to regression after methylthiouracil treatment as the diffuse form. In this case there will be, no doubt, a greater inclination both with patient and doctor towards an operation, although it must be appreciated that it is just in these cases that the cosmetic result is often less fortunate.

How far the frequency of relapses will come to influence the future attitude towards the two methods of treatment cannot yet be fully realized. The relapse frequency after subtotal thyroidectomy has varied considerably from place to place—from 2.2 per cent to 20.6 per cent, within the last five years (17). As regards the continuous methylthiouracil treatment there are only the purely provisional results to go on, because we must wait for the lapse of years. Up to the present we estimate we have had relapses in about 9 per cent of the cases but it is to be expected that more will appear in the future. However it should be pointed out that the relapses in the course of the medical treatment are so easy to deal with that they are not a serious menace. As soon as the first indication of a relapse arises, renewal of the treatment with relatively small doses for a time will cause the symptoms to disappear again.

## SUMMARY

An after-investigation has been made on 190 patients with thyrotoxicosis treated continuously with methylthiouracil, which the authors consider to be better suited to the purpose than propylthiouracil. The patients were in the hospital when the treatment was started but continuation treatment was carried on in the out-patient department. The administration of methylthiouracil lasted on an average twelve months. In 2 patients the treatment was contraindicated on account of tracheal compression; in 13 patients it had to be abandoned because of hypersensitiveness to methylthiouracil; and in 5 patients from lack of cooperation.

At the after-examination 111 patients had been without treatment for more than three months. Ten of these, or about 9 per cent, had genuine relapses and treatment was started again. All the thyrotoxic symptoms diminished or disappeared *during* the treatment. *After* the treatment was completed there was a tendency for the goiter to decrease in size and eventually to disappear.

Prolonged methylthiouracil treatment counteracts thyrotoxicosis and shortens the duration of the disease itself. Despite the chance of relapse,

which can be controlled by renewed treatment, it seems possible to achieve a permanent cure of thyrotoxicosis.

REFERENCES

1. Astwood, E. B.: Treatment of hyperthyroidism with thiourea and thiouracil, *J.A.M.A.* **122**: 78–81 (May 8) 1943.
2. Beierwaltes, W. H., and Sturgis, C. C.: Remissions in thyrotoxicosis after discontinuing thiouracil, *J.A.M.A.* **131**: 735–738 (June 29) 1946.
3. Frisk, R.: Treatment of hyperthyroidism with methylthiouracil, *Acta med. Scandinav.*, Fasc. II. **129**: 164–183, 1947.
4. Frisk, R.: Metyltiouracilbehandling af hyperthyreos, *Nord. Med.* **31**: 1575–1582 (July 19) 1946.
5. Himsworth, H. P.; Morgans, M. E., and Trotter, W. R.: Thyroidectomy and thiouracil in toxic goitre; interim comparison, *Lancet* **1**: 241–243 (Feb. 15) 1947.
6. Lundbaek, K.: Kliniske erfaringer med metyltiouracilbehandling af thyreotoxicose, *Nord. Med.* **30**: 982–984 (May 3) 1946.
7. Meulengracht, E.; Kjerulf-Jensen, K., and Schmith, K.: Metyltiouracilbehandling som kontinuerlig behandling ved morbus basedowii, *Nord. med.* **32**: 2806–2809 (Dec. 6) 1946.
8. Meulengracht, E., and Schmith, K.: Treatment of thyrotoxicosis with methylthiouracil, *Acta med. Scandinav.* **122**: 294–314, 1945.
9. Meulengracht, E.: Increasing incidence of hyperthyroidism in Denmark, *Acta med. Scandinav.* **121**: 446–459, 1945.
10. Iversen, Kurt: Temporary Rise in the Frequency of Thyrotoxicosis in Denmark 1941–45, Copenhagen, Rosenkilde and Bagger, 1948.
11. Grelland, R.: Thyrotoxicosis at Ullevål Hospital in the years 1934–1944 with special view to frequency of the disease, *Acta med. Scandinav.* **125**: 108–138, 1946.
12. Kjerulf-Jensen, K., and Meulengracht, E.: Nogle erfaringer med propyltiouracil ved behandling af morbus basedowii, *Nord. med.* **32**: 2809–2811 (Dec. 6) 1946.
13. Wahlberg, J.: On the practical importance of the clinical determination of the basal metabolic rate in thyrotoxicosis, *Acta chir. Scandinav.* **93**: 410–415, 1946.
14. Sørensen, Fr.: Mortaliteten ved basedowoperation, *Nord. med.* **27**: 1653, 1945.
15. Bertelsen, A., and Christensen, E.: Mortality, operative complications and recurrence frequency in the surgical treatment of thyrotoxicosis, *Acta chir. Scandinav.* **96**: Suppl. 133. 11–55, 1947.
16. Van Winkle, W., Jr., and others: The clinical toxicity of thiouracil: a survey of 5,745 cases, *J.A.M.A.* **130**: 343–347 (Feb. 9) 1946.
17. Brunn, E.: Mortality, operative complications and recurrence frequency in the surgical treatment of thyrotoxicosis; recurrent thyrotoxicosis, *Acta chir. Scandinav.* **96**: Suppl. 133: 56–79, 1947.

# VARIATIONS IN WHITE BLOOD CELLS FOLLOWING THE ORAL ADMINISTRATION OF GLUCOSE TO DIABETICS AND NONDIABETICS*

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## INTRODUCTION

IN 1944, Dougherty and White (1) reported that the administration of adrenocorticotropic hormone (ACTH) or the 11-oxygenated corticosteroids resulted in a diminution in the number of circulating lymphocytes in mice, rats and rabbits. Recently, Forsham *et al.* (2) have reported similar results following the administration of ACTH to 100 patients and normal subjects. This was accompanied by an increased renal excretion of sodium, chloride, potassium, uric acid, and 17-ketosteroids. The maximum effect appeared four hours after the hormone was administered.

Long (3) and Selye (4) have postulated that exposure to stress, through the mediation of the pituitary, results in increased adrenal cortical secretion. Pincus and his collaborators (5, 6, 7) have demonstrated that the exposure of normal human subjects to stress (*e.g.* increased temperature and psychomotor stress) causes a decrease in the number of circulating lymphocytes and an increased excretion of urinary 17-ketosteroids. The same workers reported a similar lymphocyte response following the oral administration of glucose. In this case no data on 17-ketosteroid excretion were presented.

The diabetogenic activity of the adrenal corticosteroids in experimental animals has been demonstrated by Long, Katzin, and Fry (8). It seemed to be of interest, therefore, to see if any differences existed in the responses of nondiabetics and diabetics to a given stress. The oral glucose tolerance test was selected for this purpose. Variations in the number of circulating lymphocytes were used as an index of response to this stress situation.

## METHOD

Thirty-two patients were studied; 14 nondiabetics, 15 diabetics, and 1 patient each with Addison's disease, Cushing's syndrome, and Sim-

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monds' disease. The ages of the patients ranged from thirteen to seventy-four years, with approximately equal distribution in the nondiabetic and diabetic groups.

All subjects were fasted for twelve to fourteen hours prior to the beginning of the study. Diabetics requiring insulin for their regulation received none on the day of the test.

A standard oral glucose tolerance test was begun at 8:30 a.m. Venous blood for sugar determinations and capillary blood for total leucocyte and

TABLE 1. MAXIMUM DECREASE IN LYMPHOCYTES AFTER ORAL ADMINISTRATION OF 100 GRAMS OF GLUCOSE, EXPRESSED IN PERCENTAGE CHANGE

| Patient | Nondiabetics | Diabetics |
|---|---|---|
| 1 | −10.9 | −51.7 |
| 2 | 11.1 | 55.9 |
| 3 | 6.0 | 32.9 |
| 4 | 20.0 | 34.5 |
| 5 | 19.3 | 32.8 |
| 6 | 16.0 | 38.7 |
| 7 | 15.1 | 38.1 |
| 8 | 22.1 | 35.8 |
| 9 | 13.9 | 36.7 |
| 10 | 10.1 | 49.3 |
| 11 | 23.7 | 41.1 |
| 12 | 40.0 | 32.5 |
| 13 | 40.2 | 28.2 |
| 14 | 8.4 | 45.6 |
| 15 | | 51.0 |
| Average | 18.3 | 43.2 |

$p = <0.01$

$m_1 - m_2/\sigma m_1 - m_2 = 81.9$

where $p$ = probability: $m$ = mean deviation: $\sigma$ = standard deviation

differential counts were taken before, and at one-half, one, two, and three hours following the administration of 100 Gm. of glucose.

Determinations were carried out in the routine manner employed at the Presbyterian Hospital, except that each white blood cell count was determined in duplicate, and three hundred cells were counted on each slide differential smear. Comparable results for the differential counts were obtained using the cover-slip method on several counts that were checked in this way.

Two of the nondiabetic and two of the diabetic subjects were restudied

under identical conditions, except that 8.0 grams of magnesium sulfate in 250 cc. of water was administered in lieu of the glucose.

## RESULTS

The blood sugar curves show the customary responses seen in diabetics and nondiabetics. This is shown in Figure 1.

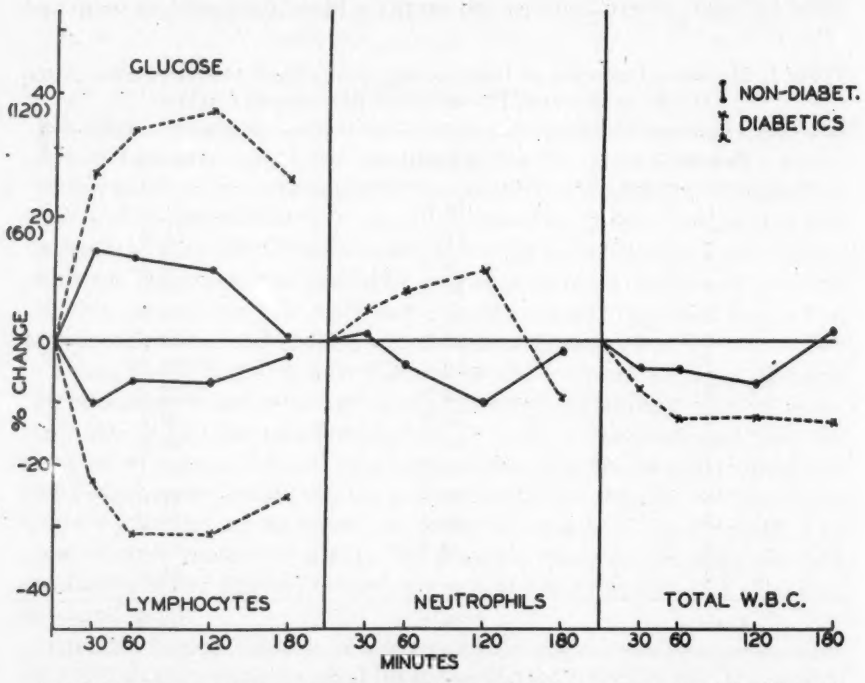


FIG. 1. Median percentage change of blood sugar, lymphocytes, neutrophils and total white blood count after the oral administration of 100 grams of glucose. The scale for the percentage change of glucose is in parentheses.

Several differences between the two groups were noted in the behavior of the total white count, absolute neutrophile, and absolute lymphocyte levels, following the oral administration of glucose. The changes in blood sugar levels and differential leucocyte counts resulting from the administration of glucose, are expressed in terms of per cent change from the control determination, which is taken as zero per cent. This method was selected because of the uniformity obtained in contrast with the wide variation in the control and test leucocyte values when expressed in absolute terms. The values plotted are the median ones for each group at the indi-

cated time intervals. Figure 1 presents a summary for the entire group of patients studied.

The number of neutrophiles appeared to increase above the control values in the diabetic group, and to decrease somewhat in the nondiabetic group. The degree of overlap in the responses of the two groups, however, would make this difference appear not to be significant. The diabetic group also displayed a greater decrease in the total white count.

The most striking difference was seen in the lymphocyte levels. The nondiabetic group showed at one-half hour the maximum percentage decrease of ten per cent from the control level. In the diabetic group, maximum percentage decrease occurred one hour after glucose and represented a decrease of 31.2 per cent. At this point there was no overlap of the central two-thirds range of values for the two groups.

Comparing the average maximum percentage decrease of the lymphocytes during the course of the glucose tolerance test, it can be seen (Table 1) that in the nondiabetic group this was 18.3 per cent, whereas in the diabetic group it was 43.2 per cent. The only overlap in this series occurred in two nondiabetic patients (numbers twelve and thirteen) in whom the diagnosis was psychoneurosis. A third such nondiabetic patient (number fourteen), however, had no such exaggerated response.

A statistical analysis of these results shows that the probability (p) is less than 0.01, and that $m_1 - m_2 / \sigma m_1 - m_2 = 81.9$, showing that the observed differences are significant (Table 1).

It was not possible to correlate the height of the blood sugar level with the percentage fall in lymphocytes in each case studied.

It was also found that the effect of the orally administered glucose was independent of the effect of any nausea that might accompany its ingestion. Hematologic studies on two nondiabetics and two diabetics, substituting 8.0 grams of magnesium sulfate for the glucose, resulted in a maximum decrease in circulating lymphocytes of only 5.8 per cent.

Though plasma volumes were not determined, the increase in the absolute number of neutrophiles in the diabetic group would indicate that the response could not be explained on the basis of an increase in blood volume with resulting hemodilution.

Several representative lymphocyte curves for normal controls, diabetics, and one patient each with Addison's, Cushing's, and Simmonds' disease respectively are shown in Figure 2. The patients with Addison's and Simmonds' diseases were given *intravenous* glucose tolerance tests. It can be seen that these two patients exhibited a response similar to that shown for the normal group (decreases of 15.1 per cent and 14.6 per cent from the control values). The patient with Cushing's disease exhibited a response similar to that of the diabetic group, her lymphocytes falling 49 per cent from the control value.

## DISCUSSION

The data presented here appear to confirm Pincus' observations that the oral administration of glucose results in a decrease in the absolute number of circulating lymphocytes. This decrease would seem to be much greater in patients with diabetes mellitus than in nondiabetics. This response seems to be independent of any nausea associated with the ingestion of glucose. It also does not appear to be due to hemodilution. The degree of

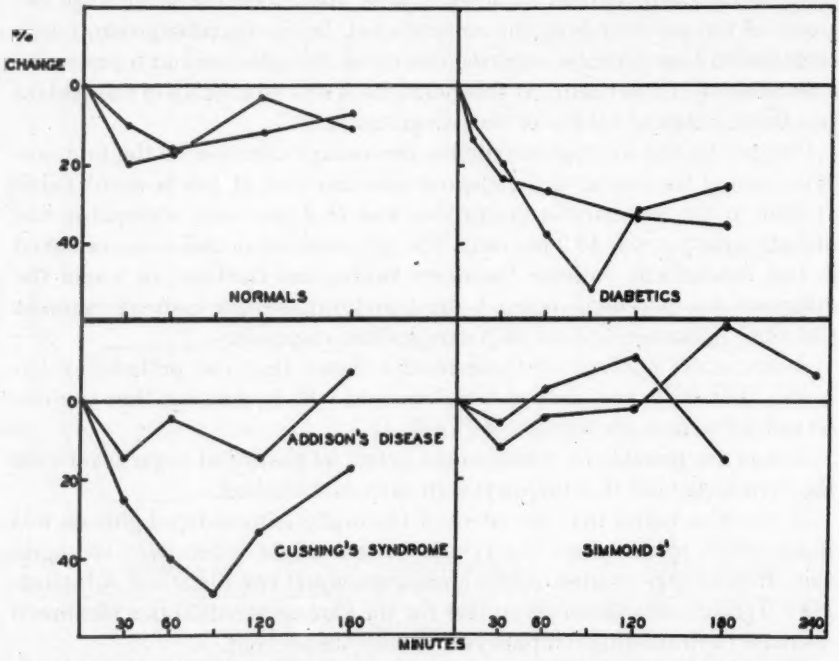


FIG. 2. Typical lymphocyte responses during oral glucose tolerance test in normal controls, diabetics, and patients with Cushing's syndrome, Addison's disease, and Simmonds' disease. (In the latter two instances, the glucose was administered intravenously).

fall, however, may not be specific for diabetics, as is shown by the overlap in the case of two psychoneurotics. Pincus (9) has also observed an exaggerated response with patients in this category.

From the data that we have accumulated to date, we have little indication as to the mechanism of action of glucose. It may be that the response of the diabetic group is a reflection of the higher blood sugar levels attained in these patients, though this is not likely in the face of the lack of correlation between blood sugar levels and decrease in lymphocyte values.

On the other hand, this difference may represent a factor inherent in the diabetic disease pattern.

As stated previously, there is evidence that exposure to stress results in the release of adrenotropic hormone, which in turn stimulates the secretion of the adrenal cortex. The fall in the level of circulating lymphocytes would appear to be compatible with an increased adrenal cortical secretion.

The fact that the patient with Addison's disease and the patient with Simmonds' disease also exhibited some decrease in lymphocytes might indicate one of the following possibilities: a) that the drop observed in the nondiabetic group is a measure of the error of the method, b) that the drop in lymphocytes under the conditions studied is not necessarily mediated by way of the pituitary-adrenal mechanism, or c) that there was still some functioning adrenal tissue present in both patients.

Thus, no direct evidence of increased secretion of adrenal hormones as a result of the administration of glucose is available from the data presented here. Work is in progress on urinary excretion of uric acid, 17-ketosteroids, sodium, and potassium, in an attempt to explore further this possibility.

There is at present no means of determining whether the fall in lymphocytes is due to their decreased production or to increased destruction, and histologic studies are necessary to clarify this point.

## SUMMARY

1. The administration of 100 grams of glucose in the form of an oral glucose tolerance test results in a decrease in the total number of circulating lymphocytes in the peripheral blood.

2. This decrease appears to be significantly greater in patients with diabetes mellitus than in nondiabetic individuals. The only exceptions occurred in two patients suffering from psychoneuroses.

3. Intravenous administration of glucose to a patient with Simmonds' disease and to one with Addison's disease produced a decrease in circulating lymphocytes similar to that observed in the nondiabetic patients.

*Acknowledgment*

The authors wish to express their appreciation to Miss Gloria Sabella for her technical assistance.

## REFERENCES

1. Dougherty, T. F., and White, A.: Influence of hormones on lymphoid tissue structure and function. The role of the pituitary adrenotrophic hormone in the regulation of the lymphocytes and other cellular elements of the blood, *Endocrinology* **35**: 1–14 (July) 1944.
2. Forsham, P. H.; Thorn, G. W.; Prunty, F. T. G., and Hills, A. G.: Clinical studies with pituitary adrenocorticotropin, *J. Clin. Endocrinol.* **8**: 15–66 (Jan.) 1948.

3. LONG, C. N. H.: The conditions associated with the secretion of the adrenal cortex, *Fed. Proc.* **6**: 461–471 (June) 1947.
4. SELYE, H.: The general adaptation syndrome and diseases of adaptation, *J. Clin. Endocrinol.* **6**: 117–230 (Feb.) 1946.
5. FREEMAN, H., and ELMADJIAN, F.: The relationship between blood sugar and lymphocyte levels in normal individuals, *J. Clin. Endocrinol.* **6**: 668–674 (Oct.) 1946.
6. HOAGLAND, H.; ELMADJIAN, F., and PINCUS, G.: Stressful psychomotor performance and adrenal cortical function as indicated by the lymphocyte response, *J. Clin. Endocrinol.* **6**: 301–311 (April) 1946.
7. PINCUS, G., and ELMADJIAN, F.: The lymphocyte response to heat stress in normal and psychotic subjects, *J. Clin. Endocrinol.* **6**: 295–300 (April) 1946.
8. LONG, C. N. H.; KATZIN, B., and FRY, E. G.: The adrenal cortex and carbohydrate metabolism, *Endocrinology* **26**: 309–344 (Feb.) 1940.
9. PINCUS, G.: Personal communication.

# CONSTITUTIONAL PRECOCIOUS PUBERTY IN THE FEMALE AND ITS CONTROL BY ANDROGENS.

## A PRELIMINARY REPORT*

S. CHARLES FREED, M.D. AND MINNIE B. GOLDBERG, M.D.
*San Francisco†, California*

THIS is a joint report of two independent endocrinologists concerned in the management of a case of precocious puberty. To our knowledge this is the first case in a female to be treated with androgens. It is being reported as a clinical experiment, the factual data being offered for consideration.

J. E. was referred to one of us (S.C.F.) at the age of 4 years and 10 months by Dr. Maurice Coleman of San Francisco because of precocious development of breasts and pubic hair. She was the only child of normal parents with a normal family history. Her birth weight and length were 6 pounds 15 ounces and 21 inches respectively. There was nothing unusual in her early development until the age of 3½ years, when her parents became aware that she was taller than her contemporaries. Soon thereafter her breasts began to develop and pubic hair appeared. At 4½ years a white vaginal discharge had been noted. The child was tall, precociously developed, of cheerful disposition and superior intelligence. Her height was 50 inches and weight, 55 pounds. Two permanent incisor teeth had erupted six months previously. Her breasts were considerably enlarged, being about 6 cm. in diameter and 3 cm. in height. The areolae were slightly pigmented. A moderate amount of pubic hair was noted. Rectal examination revealed a uterus, slightly large for a child, but no adnexal masses. A heavy caseous vaginal discharge was present. This, on microscopic examination, disclosed fully cornified mucosal cells. The physical findings were otherwise normal. Bone age studies showed a skeletal development of approximately 7 years.

Because of lack of evidence of an ovarian tumor or intracranial lesion, and because of the highly estrogenic type of vaginal smear, it was concluded tentatively that this child represented an instance of constitutional precocity as described by Novak (1). The parents, however, were most apprehensive over the possible effect of this condition on the child's psychologic development, and for this reason agreed to proceed with a phys-

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iologic experiment calculated to control the abnormal process. On the theoretical basis that androgens might hold in check those changes due to estrogen elaboration, methyltestosterone orally was prescribed. A dose of 10 mg. daily was given for one week, and 5 mg. daily thereafter. Within six weeks there was definite atrophy of the breasts and disappearance of the vaginal discharge. Vaginal smears revealed only infantile cells. Pubic and vulval hair increased and slight acne appeared. It was decided to use the appearance of acne as the gauge of dosage. Upon reduction of the dose of methyltestosterone to 5 mg. every other day, the acne disappeared. The patient was closely followed for nine months on this therapy, the sexual development remaining stationary. About this time the parents and the referring physician became alarmed over the noticeable enlargement of the clitoris and the excessively rapid skeletal growth which had occurred. She was for this reason referred to the junior author for an opinion.

At the age of 5 years and 10 months, she was a tall, pleasant, cooperative, well adjusted, very feminine-looking child, unusually intelligent for her age, and without complaints. Her measurements were as follows:

| | |
|---|---|
| Height | 54 inches (Normal range 39–50 inches) |
| Weight | 69 pounds |
| Span | 52½ inches |
| Lower body length | 25¾ inches |
| Upper body length | 28½ inches |
| Ratio of upper to lower body measurement | 1.09 |

The breasts showed slight development with a preadolescent type of nipple (Fig. 1). There was considerable pubic and vulval hair, but none in the axillae. The clitoris was about 0.5 cm. in length and was covered by a hood approximately 2.5 cm. in length. The labia were not hypertrophied. Rectal examination disclosed a uterus about 3 cm. in length and a cervix about 1.5 cm. in diameter. No adnexal masses were felt. Vaginal smears showed immature cells only. The dentition was somewhat advanced, there being six permanent anterior teeth and three permanent molars. The ocular fundi and perimetric fields were normal. The blood pressure was 90/60. The physical examination otherwise revealed nothing abnormal except for a marked lordosis.

Testosterone therapy was discontinued so that the patient might be studied and evaluated. Roentgenographic studies revealed no abnormalities of the skull, normal intravenous pyelograms save for the incidental observation of incomplete fusion of the spine of the last lumbar body and the first sacral segment, and a bone age of about 7 years and 9 months. Urinary gonadotropin assay[1] twenty-two days after cessation of therapy

[1] Method of Klinefelter, Albright and Griswold (2)

was positive at 3.2 m.u. per 24 hours, and negative at 19 m.u. per 24 hours. This is interpreted as a high value for the chronologic age, although not for the degree of sexual maturity. Urinary 17-ketosteroid determination[2]

CONSTITUTIONAL PRECOCIOUS PUBERTY

J. E., aged 5 years 10 months

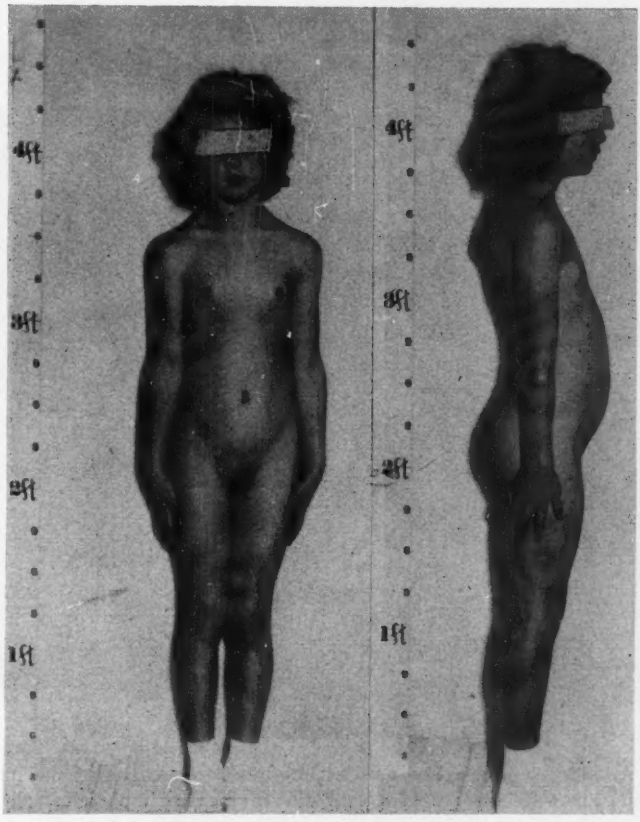


FIG. 1. After androgen therapy for 10 months. Height 54 inches (Normal range 39–50 inches); Bone age, 7 years. *Note:* slight breast development and small amount of pubic hair.

twenty-six days following cessation of therapy showed 2.4 mg. per 24 hours (ketonic fraction). The average value for an 8-year-old child is 1.0 mg. with a range of 0–2.0 mg., for this fraction (4).

[2] Method of Pincus (3).

Sixteen days following cessation of testosterone therapy, there appeared marked enlargement of the left breast with considerable induration and tenderness. One week later non-tender swellings were found in the right breast. There was questionable enlargement of the right ovary by rectal

CONSTITUTIONAL PRECOCIOUS PUBERTY

J. E., aged 7 years

FIG. 2. After 2 years of treatment with methyltestosterone. Height, 58½ inches; bone age 11 years, 3 months. *Note:* rapid skeletal growth; increase in pubic hair; little change in breasts.

examination and slight increase in uterine size. Vaginal smears showed cells characteristic of the mature vagina. The impression was that this case probably was one of the constitutional precocity type, but that the presence of an ovarian tumor or cyst had not been excluded (5). Pelvic exploration was recommended but refused by the family.

In view of the alarming rapidity of the change observed in this child's breasts and pelvis upon cessation of androgen therapy, and since explora-

tion was refused, it was recommended that the patient return to S.C.F. for continuation of androgenic therapy. Upon the resumption of a daily dose of 5 mg. of methyltestosterone orally, there was a gradual recession of the breast and vaginal changes.

In November, 1947, at the age of 6 years and 9 months, she was again seen by M.B.G. She was a very tall (height 58¼ inches) precocious-looking child with the facies of a 12-year-old (Fig. 2). Her voice was low pitched

Constitutional sexual precocity
treated with methyltestosterone

After 10 months of treatment After 2 years of treatment

FIG. 3. *Note:* moderate increase in size of clitoris and amount of pubic and vulval hair.

and slightly husky but still feminine. A suggestion of acne was present on the nose. The breasts had shown very little change in the year. A minimal amount of axillary hair was present, but the pubic hair had increased considerably (Fig. 3). There was no evidence of increased body hair elsewhere. The clitoris had grown to about 2.5 cm. in length. There was still a questionable enlargement of the ovary on the right, though the uterus and cervix were small.

In February, 1948, at the age of 7 (height 58½ inches), her bone age was estimated at 11 years and 3 months with ample growth potential remaining in the long bones. In April 1948, it was decided to stop androgenic therapy since further voice changes were undesirable and might become irreversible To date sexual development has been progressing but, thus far, menstruation has not occurred.

## DISCUSSION AND CONCLUSIONS

Although the two authors disagreed about the correct management of the case, and each is well aware of the dangers of drawing conclusions from single cases, nevertheless both are agreed that 1) androgenic therapy has definitely held in abeyance for over 2 years, breast and genital development and postponed the onset of the menarche in this case, thus obviating to a certain extent the psychologic trauma frequently associated with precocious puberty; and 2) androgenic therapy in the dosages used has produced only minimal signs of virilism, none of which is important. It should be emphasized that special care was taken to keep the dosage just below that which would produce acne.

Finally, the speculation is advanced that androgenic therapy has both stimulated skeletal growth and at the same time neutralized the influence of the estrogens on epiphysial closure so that in all likelihood this patient will not end up with the short stature so characteristic of sexual precocity.

Although it is a commonly accepted observation that precocious maturity leads to short stature because of early closure of the epiphyses of the long bones, adequate statistics are unavailable on this point. Study of the photographs of the older girls in Novak's series would tend to bear out this impression, although in only one case is the height given in conjunction with the bone age. In this case, a girl aged 10 with closed epiphyses, the height was 55¾ inches. Another patient aged 20 from the University of California Hospital Clinic, whose menarche had occurred at 5 years reached an ultimate height of 55 inches. In our case, a height of 58½ inches with a bone age of 11 years augurs well for attainment of better than minimal normal stature. If this be true, and if it be the only positive benefit derived, androgenic therapy will have been justified.

## REFERENCES

1. Novak, Emil: Constitutional type of female precocious puberty with report of 9 cases, *Am. J. Obst & Gynec.* **47**: 20–42 (Jan.) 1944.
2. Klinefelter, H. F., Jr.; Albright, F., and Griswold, G. C.: Experiences with a quantitative test for normal or decreased amounts of follicle stimulating hormone in the urine in endocrine diagnosis. *J. Clin Endocrinol.* **3**: 529–544 (Oct.) 1943.
3. Pincus, G.: The analysis of human urines for steroid substances, *J. Clin. Endocrinol.* **5**: 291–300 (Sept.) 1945.

4. TALBOT, N. B.; BUTLER, A. M.; BIRMAN, R. A.; RODRIQUEZ, P. M., and MACLACHLAN E. A.: Excretion of 17-keto steroids by normal and by abnormal children, *Am. J. Dis. Child.* **65**: 364–375 (March) 1943.
5. GOLDBERG, MINNIE B.; MAXWELL, ALICE F., and SMITH, PEARL N.: Three unusual endocrinopathies with associated ovarian pathology: I. Ovarian agenesis. II. Precocious puberty. III. Virilism, *J. Clin. Endocrinol.* **7**: 11–29 (Jan.) 1947.

# Endocrine Review

## ETHINYL ESTRADIOL

KENNETH WADE THOMPSON, M.D.*

THE estrogenic properties of what is now regarded as the most potent oral estrogen, ethinyl estradiol,[1] were first reported in Germany in January 1938, by Inhoffen and Hohlweg (2).[2] The synthesis of this substance was announced a few months later by Inhoffen *et al.* (3).[2] The initial brief publication cited data which showed that in castrated rats this substance was as active as $\alpha$-estradiol on subcutaneous injection, and it did not lose nearly as much of its activity on oral administration as $\alpha$-estradiol. Their data on the effective dose (in gammas) in castrated rats are as follows:

| | Subcutaneously Gamma | Orally |
|---|---|---|
| Ethinyl estradiol | 0.1 | 3.0 |
| $\alpha$-Estradiol | 0.1 | 50.0 |
| Estrone | 0.83 | 60.0 |
| Estriol | 10.0 | 10.0 |

In August, 1938, Clauberg and Üstün (4)[3] also in Germany reported the action of this new estrogen in 11 patients. Their interest was chiefly to show whether it had estrogenic properties rather than to work out the finer points of minimal effective dosages and untoward effects. They showed that ethinyl estradiol produces all the principal actions of $\alpha$-estradiol, for they observed it to cause uterine growth, endometrial proliferation, withdrawal bleeding, and tubal growth. The doses they utilized were very much higher than subsequently were found to be advantageous, but they estimated that the oral dose is possibly only two to three times the dose by injection.

Shortly after this, the following two publications appeared in England, *viz.:* Parkes, Dodds, and Noble (5, 6) reported in September, 1938 that ethinyl estradiol interrupted established pregnancy in rabbits. Emmens (7) in 1939 reported assays of the activity of ethinyl estradiol in ovariec-

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* Medical Director, Roche-Organon, Inc., Nutley, New Jersey.

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tomized mice, and his data indicated that in mice this substance was not as active orally as it had been in rats in the hands of Inhoffen and Hohlweg. The minimal response he obtained by injection was with 0.02 gamma, and orally with 1.2 gamma; thus, in mice, the oral dose was 60 times the parenteral dose.

Clinical reports on the use of ethinyl estradiol then began to be published in the United States. The original reports of an estrogenic activity parallel to that of $\alpha$-estradiol were confirmed. The early reports mentioned dosages that are now regarded as far too high because the extreme degree of oral effectiveness in human beings, which only gradually was apparent, was not anticipated, even though the original animal experiments showed this tendency. With higher dosages, undesirable effects, particularly gastrointestinal upsets and uterine congestive bleeding were evident. During this period there was concern lest this extraordinary estrogenic activity be harmful and, indeed, this possibility was the subject of an editorial (8) in the *Journal of the American Medical Association*. All this may have retarded progress with this drug, for several years passed before the clinicians lowered the dosage to the present recommended (9) values of from 0.03 mg. to 0.05 mg. daily. When this was done the incidence of undesirable effects was reduced to the vanishing point. There still remains some difficulty when physicians, who are not accustomed to prescribe estrogens in terms of only a few hundredths of a milligram, prescribe too great a dosage for too long a time.

Ethinyl estradiol is now being applied therapeutically in all situations in which the natural estrogens are used. There is a trend at present to use very high dosages of this and other estrogens in several experimental situations in pregnancy and cancer.

With the above brief resumé of the present status of ethinyl estradiol, we shall now consider some of the special aspects in greater detail.

## POTENCY

The biological assays in both animals (2, 10) and in man (11, 12) indicate the potency of this steroid on injection is on a par with that of $\alpha$-estradiol. This represents 120,000 *international units* per mg. The oral activity apparently varies in different species of animals, being nearly equal or equal to the injection-potency in man (11) but only 1/30th of the injection-potency in rats (3) and only 1/60th in mice (7). There is room for further animal assays, since they are few and were carried out years ago by different investigators. The extreme activity in man on oral administration is decidedly exceptional in comparison with all other estrogens, including the stilbene derivatives; for example, the oral dose of diethylstilbestrol is roughly five times the parenteral dosage (Israel (13)).

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### DURATION OF ACTION

There is little specific published information available on the duration of action of ethinyl estradiol in man, save the following: The tables shown in the report of Soule (12) indicate that withdrawal bleeding occurred on the sixth to seventh days after stopping the oral dosage. This is in agreement with observations of Salaber and del Castillo (14) who noted that withdrawal bleeding began five to six days after cessation of treatment. This indicates there is hardly any prolongation of the action of the drug in the body, and speaks against any supposition that ethinyl estradiol is protected for long from inactivation by the ethinyl group.

In a report on urinary estrogen excretion Stealy and Stimmel (15) cite one study in which they orally administered 1 mg. of ethinyl estradiol to a bilaterally orchiectomized man, and in the ensuing forty-eight hours they were unable to detect measurable amounts of estrogen in the urine. In similar periods sizeable proportions of doses of $\alpha$-estradiol benzoate and of estrone were eliminated in the urine, as were lesser but measurable amounts of estradiol benzoate and dipropionate. It is hardly possible to ascribe meaning to this result with ethinyl estradiol save to say that this seems to be a profitable approach and more data are needed.

Segaloff (16) in a study of the potency of estrogens in relation to inactivation by the liver, utilizing splenic implants, found that ethinyl estradiol is inactivated by the liver in approximately the same degree as $\alpha$-estradiol. It was found to be "far the most active derivative of estradiol tested," and Segaloff considered that its effectiveness when given orally results from its high degree of estrogenic activity rather than from any resistance of this substance to inactivation by the liver.

### THERAPEUTIC USES

Ethinyl estradiol has been reported to have been prescribed in practically every situation for which oral estrogens are therapeutically utilized currently; as for example, for relief of menopausal symptoms (9 and 17–31); the production of withdrawal bleeding in amenorrhea (4, 11, 12, 32, 33, 34); the relief of dysmenorrhea (35); the treatment of acne (36); the prevention of lactation and of breast engorgement in the puerperium (17, 37); therapeutic suppression of cancer of the prostate in men (38–44) and of the breast in elderly women (45); also, it is now being used in various experimental situations, one of which is the induction of labor (17).

*Menopausal symptoms* were relieved, with very few exceptions, and a report published in 1946 by Weisbader and Filler (9) is representative of the present tendency to use smaller doses than formerly. These authors studied 53 menopausal patients whose symptoms were satisfactorily relieved in from six to nine days after starting therapy. The initial dosage

of 0.05 mg. three times daily was reduced to 0.05 mg. once daily when they discovered that this lower dosage controlled the symptoms and avoided associated gastro-intestinal upsets ascribed to the steroid. These authors mentioned that the patient may become accustomed to the drug and the dose might later be increased without untoward symptoms. Their vaginal smear studies and endometrial biopsies confirmed the therapeutic action.

*Withdrawal bleeding* is readily produced by this estrogen. Allen (11) reported that 0.40 mg. per week was sufficient to produce withdrawal bleeding in his series, and he drew a comparison of this effect with other estrogens, *viz.:*

| | |
|---|---|
| Ethinyl estradiol, orally | 0.40 mg. per week |
| α-Estradiol, orally | 13.40 mg. per week |
| Estradiol dipropionate, intramuscularly | 0.86 mg. per week |
| Estradiol monobenzoate, intramuscularly | 1.06 mg. per week |
| Estradiol monopropionate, intramuscularly | 1.75 mg. per week |
| Estrone, orally | 31.50 mg. per week |
| Estrone, intramuscularly | 3.00 mg. per week |
| Sodium estrone sulfate, orally | 17.50 mg. per week |
| Stilbestrol, orally | 3.00 mg. per week |
| Mono-methoxy stilbestrol, orally | 35.00 mg. per week |
| Dimethoxy stilbestrol, orally | 14.00 mg. per week |
| Hexestrol, orally | 10.50 mg. per week |
| Sodium estriol glucuronidate, orally | 42,000 "oral" units per week |
| Mixed estrogens, orally | 126,000 I. U. per week |

Soule (12) reported that doses of 0.05 mg. per day for twenty-one days produced withdrawal bleeding in two patients and half this dose was effective in one patient. The reports indicate that the bleeding occurs on the fourth to seventh days after the drug is stopped (12, 14).

Congestive bleeding due to overdosage of the drug or to prolonged treatment has been fairly common with this as it has been with other active estrogens. For this reason both Allen (11) and Lyon (35) and many others have recommended planned episodes of withdrawal bleeding in order to shed the endometrium and thus to avoid an episode of congestive bleeding. Should overdosage bleeding occur, it is necessarily followed by withdrawal bleeding when the dosage of the drug is reduced.

*Acne* has been treated by Lawrence and Werthesson (36) who reported considerable success with ethinyl estradiol (freedom from acne in 15 of 25 patients), with no unpleasant reactions. Two of the 11 males developed gynecomastia. The dosage was 0.05 mg. daily, increased to 0.30 mg. if the response was not satisfactory.

*The relief of essential dysmenorrhea* by the administration of ethinyl estradiol early in the menstrual period has been reported by Lyon (35). He studied 138 cycles of 12 women who suffered from dysmenorrhea. In 44

cycles ethinyl estradiol was administered for from twenty-one to twenty-four days, starting early in the cycle. The dosage was 0.05 mg. daily. This treatment inhibited ovulation, as was shown by basal body temperature graphs. During these cycles, if so treated, the patients had relief of dysmenorrhea. Successive cycles were managed in this manner with relief of the dysmenorrhea. Lyon evolved a plan by which he inhibited ovulation with the treatment for two successive cycles and then, in the next cycle, he permitted ovulation to occur.

*Prevention of lactation and breast engorgement* by therapy with ethinyl estradiol has been reported by Kurzrok and associates (37). They stated that the factors required for success were that the medication be started early, before lactation is actually under way. With dosage of from 1.8 mg. to 2.4 mg. daily for from three to four days, the results were termed excellent with only 9 failures in 26 cases. When the therapy was started after lactation had begun, there was a reduction in the breast engorgement which occurs after nursing is stopped.

In a later, more complete study, Birnberg *et al.* (17) reported further efforts on suppression of lactation in 145 non-nursing and in 26 nursing mothers. The treatment was started within twenty-four hours after delivery, with the administration of two tablets (each 0.05 mg.) three times daily during the first three days; one tablet, three times daily during the next three days; and one tablet once daily during the last three days. No other medication was given, and no breast support was provided unless the result was poor. The results were classed as follows: excellent, 58 per cent; good, 16 per cent; fair, 16 per cent; and poor, 10 per cent. In the 26 nursing mothers there was complete suppression in 6; partial, in 17; and no effect in 6. A few of the patients (5 of 165) noticed some withdrawal bleeding after the drug was stopped.

*Suppression of cancer of the prostate* with ethinyl estradiol has been widely used as therapy following reports by Kearns (39, 40) and by McCrea (41) and others (38). This estrogen lowers the phosphatase as do other estrogens (42). The dosage employed by McCrea (41) was 0.05 mg. daily, or three times daily, for thirty days, succeeded by a rest period of thirty days. There are current indications, as yet unpublished, which may indicate that dosages higher than the above may give further control when the cancer appears to be breaking out of the control afforded by the smaller doses mentioned here.

*Regression of certain cancers of the breast* following high dosages of ethinyl estradiol has been reported by Herrmann, Adair and Woodward (45) and by others.[4] The favorable response appeared in older women (aged over

[4] Address by Dr. Ira. T. Nathanson before the American College of Surgeons, December 18, 1946.

60 years), and the improvement was shown by a healing of local ulcerations and a reduction of the size of pulmonary metastases and of skin metastases. The dosage of ethinyl estradiol was from 0.15 mg. to 0.07 mg. per day, continued until improvement was evident. The status of this therapy is not yet established, for the whole matter of giving estrogen to women with breast cancer is fraught with danger because in the younger women the cancerous growth has been accelerated by estrogens (38). Also, in others, there may be a dangerous flooding of the body with calcium, as is the case in certain patients treated with testosterone. This steroid has been included among those to be appraised by the Subcommittee on Steroids in Breast Cancer, of the Council on Pharmacy and Chemistry of the American Medical Association.

*The induction of labor* with ethinyl estradiol was reported by Birnberg *et al.* (17) in 1947, and indeed this effect was predicted in an editorial in the *British Medical Journal* (46) in 1938. Birnberg and associates (17) used ethinyl estradiol in 49 women at or near term: to induce labor in 15, and to hasten a nonprogressive labor in 34. The dosage used was six tablets, 0.05 mg. each, every two hours until 15 doses had been given. "There were no side effects as a result of this treatment." In the 15 women the treatment to induce labor was followed by labor in 10, and was without effect in 5. In the 10 successful cases, 5 patients were delivered within twelve hours after the start of the treatment and the remaining 5 were delivered before the thirtieth hour. In the 34 "nonprogressive" patients the therapy successfully hastened delivery in 30, and was without effect in 4. In the 30 hastened labors, delivery was within twelve hours in 26 and within twenty hours in 4.

It is obvious that this first clinical report on this subject represents merely the beginning of an approach to the problem, for the difficulties of judging any process aimed to accelerate labor are quite apparent. Nevertheless, this very important possible action deserves further appraisal. It is not illogical, in view of the evidence, to suppose that there is normally a sharp increase in the nondegraded estrogens in blood and urine at term.

*Chronic hemospermia* is a disorder in which blood originates in the seminal vesicles, and Huggins and McDonald (47) utilized ethinyl estradiol to suppress the function of the vesicles. They state that since the prostate has a lower threshold of sensitivity to androgen than do the seminal vesicles, it is possible by adjusting the estrogen dosage to suppress the vesicle secretion and thereby eliminate the bleeding, without noticeably reducing the prostatic secretion. This dosage also reduced the sperm count.

Six patients were treated, and the dosage was varied according to the response; the usual 0.05 mg. tablet of ethinyl estradiol was taken at intervals of from twice weekly to twice daily, for periods of from three to seven

weeks. In two cases there was breast engorgement. One patient showed no response to the estrogen. In 1 case the bleeding returned after three months but in 4 of the 6, the bleeding apparently was fully arrested.

### THE UNDESIRABLE ACTIONS OF ETHINYL ESTRADIOL

When the dosage of ethinyl estradiol in women is increased above 0.10 mg. per day, there is an increasing incidence (8, 17–26, 48–51) of undesirable actions, such as gastro-intestinal upsets (nausea or vomiting, which come on soon after the initial high dose), headaches, congestive vaginal bleeding (which occurs variably after a number of weeks of treatment), tingling and sensitivity of the breasts and nipples and, with extreme doses after prolonged treatment, marked pigmentation of the skin of nipples, abdomen, and axillae. In males, gastro-intestinal upsets are almost uniformly absent (38–41) even with higher dosages, but there is some tendency to gynecomastia (36, 39, 40, 41), possibly less with this estrogen than with stilbestrol (39, 40). There is one report (27) of urticaria following this estrogen, but the urticaria was not traced directly to the steroid.

These undesirable reactions are shared by the estrogens which are most active on oral administration, and it may be that this effect is inherent in their estrogenic properties. The congestive vaginal bleeding, gynecomastia, and pigmentation of the skin should not be regarded as undesirable signs for they are evidence of the very active estrogenic action; and treatment should be adjusted accordingly.

The gastro-intestinal upsets produced by higher dosages of ethinyl estradiol are apparently real, and the evidence, although meager in published reports but extensive in the experience of many clinicians, indicates that the nausea or vomiting is often only a temporary upset; and with persistence of the dosage, these symptoms will usually cease after a few days. It is said that should a woman persistently be upset by one estrogen, she is also intolerant to others.

No data are available on the pathological physiology of this disturbance. Whether the action is local on the gastro-intestinal muscle and sphincter mechanisms, or is an effect on the biliary passages through which possibly a considerable portion of the estrogen may be excreted, or is a central nervous disturbance, or is some hitherto unmentioned possibility, remains to be investigated.

This matter assumes considerable importance now that very large doses (as much as 2.0 mg. per day) are visualized in the treatment of patients with cancer. The gastro-intestinal disturbance may determine the success or failure of the treatment.

It is clear that gastro-intestinal upsets occur only rarely in women when the dosage is 0.05 mg. per day or less (9, 23); or, with various dosages in

men, when used for prostatic cancer. Pregnant women at term appear to tolerate large doses well, for Birnberg *et al.* (17) have reported the administration of 0.3 mg. every two hours for a total of 15 doses, and observed no ill effects. Should one venture for special reasons to use high doses of this drug early in pregnancy it would be well to start with small dosages and increase only gradually, for in animals estrogen is toxic to the early fetus, and Dr. Olive Smith[5] has recently reported that stilbestrol in certain high doses may be toxic to the early human fetus.

## CONCLUSION

The foregoing review of the data available on ethinyl estradiol indicates that this steroid is the most potent oral estrogen known and has therapeutic effects similar to $\alpha$-estradiol. In man this steroid on oral ingestion appears to be spared initial destruction by the intestine and the liver. However, just how the ethinyl group enhances the oral activity is not known, for studies with splenic implants in rats indicate that ethinyl estradiol is inactivated by the liver at much the same rate as is $\alpha$-estradiol. Perhaps there is a species difference in this respect. Although there is increasing clinical use of this estrogen in conventional therapeutic indications, based upon well established evidence of its estrogenic activity, there is a relative paucity of information on the more subtle details of its fate in the various parts of the body such as its site of inactivation, degradation products, path of excretion and effect on the pituitary. Obviously this important substance deserves further investigation.

## SUMMARY

The literature on ethinyl estradiol has been reviewed. This estrogen has an estrogenic activity similar to $\alpha$-estradiol, and its oral potency approaches its injection potency. The activity is thus comparable to 120,000 *international units* per mg. It has been prescribed in all situations for which estrogens are currently utilized in therapy. There is need for further information concerning the more subtle details of its fate, such as pathways of excretion, the cause of gastro-intestinal disturbances sometimes produced by higher doses such as are now used in cancer cases, and the reasons for the sparing of its activity by the ethinyl group. A list of all known references is given.

## REFERENCES

1. Selye, H.: Enclyclopedia of Endocrinology, Montreal, Canada, A.W.T. Franks Publishing Co., vol. 1, p. 95.
2. Inhoffen, H. H., and Hohlweg, W.: Neue per os-wirksame weibliche Keimdrü-

[5] Address before the Norfolk Co. Medical Society, Boston, Mass., February 24, 1948.

senhormonderivate: 17-Aethinyl-oestradiol und Pregnen-in-on-3-ol-17, *Naturwissenschaften* **26**: 96 (Feb. 11) 1938.

3. INHOFFEN, H. H.; LOGEMANN, W.; HOHLWEG, W., and SERINI, A.: Untersuchungen in der Sexualhormen-Reihe, *Ber. deut. chem. Ges.* **71**: 1024–1032 (May 4) 1938.
4. CLAUBERG, C., and ÜSTÜN, Z.: Menstruation—per os erzeugt. Beweise der Wirksamkeit von Progynon C, einem neuen Follikelhormonderivat, und Proluton C, einem neuen Luteohormonpräparat, bei peroraler Verabreichung, *Zentralbl. f. Gynäk.* **62**: 1745–1761 (Aug. 6) 1938.
5. PARKES, A. S.; DODDS, E. C., and NOBLE, R. L.: Interruption of early pregnancy by means of orally active oestrogens, *Brit. M. J.* **2**: 557–559 (Sept. 10) 1938.
6. ANNOTATIONS: Artificial oestrogens, *Lancet* **2**: 686–687 (Sept. 17) 1938.
7. EMMENS, C. W.: The oral activity of certain androgens, oestrogens and augmenting substances, (Proc. Physiol. Soc., Dec. 10, 1938), *J. Physiol.* **94**: 22P–23P, 1939.
8. EDITORIAL: Estrogen therapy—a warning, *J.A.M.A.* **113**: 2323–2324 (Dec. 23) 1939.
9. WIESBADER, H., and FILLER, W.: Oral therapy with ethinyl estradiol in the menopause, *Am. J. Obst. & Gynec.* **51**: 75–81 (Jan.) 1946.
10. MORGAN, C. F., and PONZIO, O. A.: Cutaneous application of ethinyl estradiol in alcohol, *Proc. Soc. Exper. Biol. & Med.* **56**: 118–120 (June) 1944.
11. ALLEN, W. M.: The biological activity of various estrogens, *South. M. J.* **37**: 270–280 (May) 1944.
12. SOULE, S. D.: Estrogen-withdrawal bleeding; a study of comparative activity of various estrogens, *Am. J. Obst. & Gynec.* **44**: 684–686 (Oct.) 1942.
13. ISRAEL, S. L.: Diagnosis and treatment of amenorrhea, *M. Clin. North America* **26**: 1831–1855, 1942.
14. SALABER, J. A., and DEL CASTILLO, E. B.: Accion del etinilestradiol derivado de la hormona folicular, por via oral, *Semana méd.* **1**: 6–10 (Jan. 5) 1939.
15. STEALY, C. L., and STIMMEL, B. F.: Further studies on the metabolism of therapeutic doses of natural estrogens in human subjects, *J. Clin. Endocrinol.* **8**: 67–75 (Jan.) 1948.
16. SEGALOFF, A.: The intrasplenic injection of some synthetic estrogens and proestrogens, *Endocrinology* **34**: 335–339 (May) 1944.
17. BIRNBERG, C. H.; LIVINGSTON, S. H.; KURZROK, L., and SHERBER, D. A.: Ethinyl estradiol, *Am. J. Obst. & Gynec.* **54**: 855–860 (Nov.) 1947.
18. BISHOP, P. M. F.; BOYCOTT, M., and ZUCKERMAN, S.: The oestrogenic properties of "stilboestrol" (diethyl-stilboestrol); a clinical and experimental investigation, *Lancet* **1**: 5–11 (Jan. 7) 1939.
19. GEIST, S. H., and SALMON, U. J.: Present status of endocrine diagnosis and therapy in gynecology, *Clinics* **1**: 1197–1215 (Feb.) 1943.
20. GEIST, S. H., and SALMON, U. J.: Recent advances in gynecologic hormone therapy, *New York State J. Med.* **41**: 2220–2227 (Nov. 15) 1941.
21. GROPER, M. J., and BISKIND, G. R.: Ethinyl estradiol: a clinical evaluation, *J. Clin. Endocrinol.* **2**: 703–706 (Dec.) 1942.
22. HARDING, F. E.: Oral substitution therapy with ethinyl estradiol and alpha-estradiol, *Am. J. Obst. & Gynec.* **48**: 181–188 (Aug.) 1944.
23. LYON, R. A.: Management of the climacteric with ethinyl estradiol, *Am. J. Obst. & Gynec.* **47**: 532–536 (April) 1944.
24. SALMON, U. J.; GEIST, S. H.; WALTER, R. I., and MINTZ, N.: Therapeutic effective-

ness of orally administered ethinyl estradiol, *J. Clin. Endocrinol.* **1**: 556–558 (July) 1941.

25. Shorr, E.: Management of the menopause, (Conferences on Therapy, Cornell University Medical College and New York Hospital), *New York State J. Med.* **41**: 2336–2345 (Dec. 1) 1941.
26. Soule, S. D.: A clinical trial of ethinyl estradiol, *Am. J. Obst. & Gynec.* **45**: 315–317 (Feb.) 1943.
27. Watson, B. A.: Clinical experiences with oral ethinyl estradiol, *J. Clin. Endocrinol.* **2**: 447–449 (July) 1942.
28. Watson, B. A.; Yolton, N., and Rauls, L.: Sex hormone assays in the menopause; their clinical significance, *J. Lab. & Clin. Med.* **28**: 732–735 (March) 1943.
29. Dodds, E. C.: The new endocrinology. IV. The female sex hormone, *Lancet* **2**: 953–954 (Oct. 28) 1939.
30. Hutton, J. H.: Diagnosis and treatment of endocrine disorders with a minimum of laboratory work, *Urol. & Cutan. Rev.* **49**: 67–70 (Feb.) 1945.
31. Karnaky, K. J.: Hydrogen ion concentration of the senile vaginal mucosa before and after estrogenic therapy, *South. M. J.* **39**: 906–907 (Nov.) 1946.
32. Emmel, V. M.; Worthington, R. V., and Allen, E.: Attempts to induce menstruation by operative ischemia in monkeys, *Endocrinology* **29**: 330–335 (Sept.) 1941.
33. Rakoff, A. E.: Studies on high dosage progesterone therapy of amenorrhea, *Am. J. Obst. & Gynec.* **51**: 480–491 (April) 1946.
34. Dunn, C. W.: Febrile hyperthyroidism, *Clinics* **3**: 337–345 (Aug.) 1944.
35. Lyon, R. A.: Relief of essential dysmenorrhea with ethinyl estradiol, *Surg., Gynec. & Obst.* **77**: 657–660 (Dec.) 1943.
36. Lawrence, C. H., and Werthessen, N. T.: Treatment of acne with orally administered estrogens, *J. Clin. Endocrinol.* **2**: 636–638 (Nov.) 1942.
37. Kurzrok, L.; Birnberg, C. H., and Livingston, S.: Use of ethinyl estradiol to prevent lactation in puerperal patients, *J. Clin. Endocrinol.* **2**: 471–472 (July) 1942.
38. Herbst, W. P.: The present picture in chemotherapy in prostatic carcinoma, *J. Urol.* **57**: 296–299 (Feb.) 1947.
39. Kearns, W. M.: Pellet implantation of hormones in urology, *J. Urol.* **47**: 587–590 (May) 1942.
40. Kearns, W. M.: Treatment of carcinoma of the prostate with estrogens, *Wisconsin M. J.* **41**: 575–581 (July) 1942.
41. McCrea, L. E.: Carcinoma of the prostate: a résumé of treatment with ethinyl estradiol; preliminary report, *J. Urol.* **56**: 697–703 (Dec.) 1946.
42. Woodard, H. Q., and Dean, A. L.: The significance of phosphatase findings in carcinoma of the prostate, *J. Urol.* **57**: 158–171 (Jan.) 1947.
43. Dean, A. L.: Carcinoma of the prostate, *Bull. New York Acad. Med.* **23**: 454–471 (Aug.) 1947.
44. Treves, N.: Problems in the postoperative care of cancer patients, *New York State J. Med.* **44**: 2248–2254 (Oct. 15) 1944.
45. Herrmann, J. B.; Adair, F. E., and Woodard, H. Q.: Effect of estrogenic hormone on advanced carcinoma of the female breast, *Arch. Surg.* **54**: 1–9 (Jan.) 1947.
46. Editorial: Experimental interruption of pregnancy, *Brit. M. J.* **2**: 580 (Sept. 10) 1938.
47. Huggins, C., and McDonald, D. F.: Chronic hemospermia; its origin and treatment with estrogen, *J. Clin. Endocrinol.* **5**: 226–231 (May–June) 1945.

48. Frank, R. T.; Goldberger, M. A., and Felshin, G.: Clinical and laboratory investigations of some of the newer sex hormone preparations, *Endocrinology* **27**: 381–384 (Sept.) 1940.
49. Freed, S. C.: Present status of commercial endocrine preparations, *J.A.M.A.* **117**: 1175–1182 (Oct. 4) 1941.
50. Harding, F. E.: The oral use of hexestrol for estrogen deficiency, *Am. J. Obst. & Gynec.* **51**: 660–665 (May) 1946.
51. Loeser, A. A.: Therapeutic trials of diethylstilboestrol, *Brit. M. J.* **1**: 13 (Jan. 7) 1939.

# Letter to the Editor

TO THE EDITOR:

## A SIMPLE TEST OF CLINICAL VALUE FOR THE DIFFERENTIATION OF TESTOSTERONE AND DESOXYCORTICOSTERONE IN PELLET FORM

IN THE course of treatment of certain endocrinopathies (*e.g.*, hypopituitarism and Addison's disease), both testosterone and desoxycorticosterone pellets are frequently implanted subcutaneously.

Subsequently pellets may be extruded because of local infection or a fault in the technique of implantation, and the question arises as to the identity of the extruded pellet. In the case of desoxycorticosterone, this is particularly important because this drug has life-saving properties in patients with hypoadrenocorticism, yet it has potential toxic reactions to these same patients when given in excessive amounts.

One of us (H. J.), on the basis of a detailed study of the color reactions of steroids (unpublished data) has suggested a rapid simple test for the identification of desoxycorticosterone and testosterone pellets that has been found useful in the clinic. A small amount of the pellet under question is crushed into a fine powder and placed in a test tube. Three drops of concentrated sulfuric acid are added, and the tube is allowed to stand for three minutes at room temperature. Three to 5 cc. of glacial acetic acid are added and the tube is shaken. In the presence of desoxycorticosterone the solution remains colorless, whereas in the case of testosterone a blue solution with an intense red fluorescence develops. Care should be taken that the reagents are strictly anhydrous and that the sulfuric acid reaction is carried out at room temperature, since desoxycorticosterone will react in the same way as testosterone at higher temperatures.

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School, Boston, Massachusetts.*

W. F. ROGERS, JR., M.D.*
HERBERT JAFFE, PH.D.
August 25, 1948

* Present address: University Hospital of the Good Shepherd, Syracuse 10, N. Y.

COMMENT:

The Editor would like to point out that extrusion of pellets is rare if they are inserted by a technique involving the use of a trocar specially designed for this purpose.

# The Association for the Study of Internal Secretions Announces A Postgraduate Assembly In Endocrinology

OKLAHOMA CITY, OKLAHOMA SKIRVIN HOTEL FEBRUARY 21–26, 1949

The faculty will consist of prominent researchers and clinical endocrinologists in the various branches of the medical sciences, gathered from the United States and Canada and will include the following:

Dr. Willard M. Allen, Professor and Head, Department of Obstetrics and Gynecology, Washington University School of Medicine.

Dr. Edwin B. Astwood, Research Professor of Medicine, Tufts College.

Dr. J. S. L. Browne, Professor of Medicine, McGill University.

Dr. Edward A. Doisy, Professor and Head, Department of Biochemistry, St. Louis University School of Medicine.

Dr. Roberto Escamilla, Associate Clinical Professor of Medicine, University of California Medical School.

Dr. E. C. Hamblen, Associate Professor of Obstetrics and Gynecology, Duke University School of Medicine.

Dr. Laurence W. Kinsell, Associate Clinical Professor of Medicine, University of California Medical School.

Dr. C. N. H. Long, Sterling Professor of Physiological Chemistry and Dean, Yale University School of Medicine.

Dr. Cyril M. MacBryde, Associate Professor of Clinical Medicine, Washington University School of Medicine.

Dr. E. Perry McCullagh, Chief, Dept. of Endocrinology and Metabolism, Cleveland Clinic.

Dr. Harold L. Mason, Professor, Physiological Chemistry, Mayo Foundation, University of Minnesota.

Dr. Warren O. Nelson, Professor of Anatomy, University of Iowa College of Medicine.

Dr. Edward Rynearson, Associate Professor of Medicine, Mayo Foundation, University of Minnesota.

Dr. Hans Selye, Professor of Experimental Medicine, University of Montreal.

Dr. E. Kost Shelton, Associate Professor of Medicine, University of Southern California.

Dr. Paul M. Starr, Clinical Professor of Medicine, University of Southern California.

Dr. Willard O. Thompson, Clinical Professor of Medicine, University of Illinois College of Medicine.

Dr. George Thorn, Hershey Professor of the Theory and Practice of Physic, Harvard Medical School.

Dr. Henry H. Turner, Associate Professor of Medicine, University of Oklahoma School of Medicine.

Dr. Lawson Wilkins, Associate Professor of Pediatrics, Johns Hopkins Hospital.

This course will be a practical one of interest and value to the specialist and those in general practice. The program will consist of lectures, clinics and demonstrations. Ample time will be given to questions and answers at the end of each session, and registrants are encouraged to contact members of the faculty for individual discussions.

A fee of $100 will be charged for the entire course and the attendance will be limited to 100. REGISTRATION WILL BE IN THE ORDER OF CHECKS RECEIVED AND WILL CLOSE ON FEBRUARY 1, 1949. Should there be an insufficient number of applicants to fill the course, the registration fee will be immediately refunded in its full amount.

Please forward application on your letterhead, together with check, payable to The Association for the Study of Internal Secretions, to Henry H. Turner, M.D., Chairman of the Postgraduate Committee, 1200 North Walker Street, Oklahoma City, Oklahoma, before February 1, 1949.

Applicants should make reservations directly with hotels of their choice. Some of the better downtown hotels in Oklahoma City, listed according to their proximity to the Skirvin are: Skirvin Tower, Huckins, Wells-Roberts, Biltmore and Black.

## ANNOUNCEMENT OF NATIONAL RESEARCH COUNCIL GRANTS FOR RESEARCH IN ENDOCRINOLOGY

The Committee on Research in Endocrinology, National Research Council, wishes to announce that requests for grants-in-aid during the fiscal period from July 1, 1949, to June 30, 1950, will be received until February 28, 1949. Application blanks may be obtained by addressing the Secretary, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C. In addition to a statement of the problem and research plan or program, the Committee desires information regarding the proposed method of attack, the institutional support of the investigation and the uses to be made of the sum requested. No part of any grant may be used by the recipient institution for administrative expenses.

The Committee makes grants-in-aid of research in the general field of experimental and clinical endocrinology. However, applications for support of research in the problems of sex in the narrower sense cannot be given favorable consideration, and investigators seeking support in this field should direct their proposals to the Committee for Research in Problems of Sex of the National Research Council. The Committee on Research in Endocrinology, however, will continue to give consideration to the support of studies of the effect of sex hormones on non-sexual functions, *e.g.*, on general metabolism and on the metabolism of steroid hormones.

# The 1949 Meeting of the Association for the Study of Internal Secretions

The Thirty-First Annual Meeting of the Association for the Study of Internal Secretions will be held in the Chalfonte-Haddon Hall, Friday and Saturday, June 3 and 4, 1949, in Atlantic City, New Jersey.

We are informed by the hotel management that reservations will be difficult to secure on short notice; therefore, members are urged to make reservations at once with Chalfonte-Haddon Hall, giving time of arrival and length of stay in Atlantic City.

The scientific sessions will be held in the Viking Room, as formerly, and registration will be on the same floor. The annual dinner will be held in the Rutland Room, Friday, June 3, at 7 p.m., preceded by cocktails in the same room.

Those wishing to present papers, which will be limited to ten minutes, should send the title and four copies of an abstract of not more than 200 words, to Dr. J. S. L. Browne, Royal Victoria Hospital, Montreal 2, Canada, not later than March 1, 1949. It is imperative that the abstracts be informative and complete, with results and conclusions, in order that they may be of value for reference and suitable for printing in the program.

Nominations for the Squibb and Ciba Awards and the Ayerst, McKenna and Harrison Fellowship should be filed on special forms with the Secretary of the Association, not later than March 15, 1949, according to specifications given in the section on Awards.

# The Awards of the Association for 1949

*Nominations for Awards*

Three Awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. A special committee of five members of the Association chooses the recipients of these Awards, subject to ratification by the Council, and each member of the Association has the privilege of making one nomination for each Award.

Nominations for the Awards should be made on special application forms which may be obtained from the Secretary, Dr. Henry H. Turner, 1200 North Walker Street, Oklahoma City 3, Oklahoma. All nominations, accompanied by a statement of the importance of the nominee's contributions to endocrinology and a bibliography of his most important papers with reprints if possible, should be sent to Dr. Turner's office not later than March 15, 1949.

## THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr. Edward A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori and in 1948 to Dr. Fuller Albright. No award was made in 1943. No age or special limitation is stipulated by the donor of the Award.

## THE CIBA AWARD

The Ciba Award, established in 1942, is given in recognition of the meritorious accomplishment of an investigator, not over 35 years of age, in the field of clinical or preclinical endocrinology. In 1944 the Award was given to Dr. E. B. Astwood; in 1945 to Dr. Jane Anne Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li and in 1948 to Dr. Carl G. Heller. The Award is for $1,200.00. If within two years of the date of the Award, the recipient chooses to use it to aid in working in a laboratory other than the one in which he normally is located, the Award will be increased to $1,800.00.

## THE AYERST, McKENNA & HARRISON FELLOWSHIP

The first Ayerst, McKenna & Harrison Fellowship was given to Dr. Samuel Dvoskin in 1947 and in 1948 it was given to Dr. Ernest M. Brown, Jr. This Fellowship is designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinology. The Fellowship may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend for the Fellowship will vary in accordance with the qualifications of the appointee, but will not exceed $2500.00. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. The nominee must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals, submit a program of proposed study, indicate one or more institutions where the proposed program shall be carried out and submit statements of approval from the investigators with whom he proposes to conduct his research.

# Award of the American Goiter Association

## THE VAN METER PRIZE

The American Goiter Association again offers the Van Meter Prize Award of three hundred dollars and two Honorable Mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Madison, Wisconsin, May 26, 27 and 28, 1949, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length, and must be presented in English. A typewritten double spaced copy should be sent to the Corresponding Secretary, Dr. T. C. Davison, 207 Doctors Building, Atlanta 3, Georgia not later than March 15, 1949. The Committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association. This will not prevent its further publication, however, in any journal selected by the author.

## THE AMERICAN COLLEGE OF PHYSICIANS ANNOUNCES THE RECIPIENTS OF EIGHT RESEARCH FELLOWSHIPS FOR 1949–1950

The Board of Regents of the American College of Physicians announces the recent appointment of eight outstanding young physicians to Research Fellowships in Medicine for the year beginning July, 1949. These Fellowships, to which appointments are made in varying numbers each year, are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching and investigative career in Internal Medicine. The recipients of the current awards are as follows:

JAMES KILGORE DEVORE, M.D., of Dallas, Tex. A graduate of Central College, Fayette, Mo., in 1943, Dr. DeVore received the M.D. degree from the University of Oklahoma School of Medicine in 1947, and interned at the State of Wisconsin General Hospital, Madison, in 1947–1948. Now a fellow in internal medicine in The Frank E. Bunts Education Institute of the Cleveland Clinic, Dr. DeVore will conduct studies next year with Drs. Irvine H. Page, F.A.C.P., and Arthur C. Corcoran, in the Research Division of the Cleveland Clinic, on the determination of the action of active adrenal steroids in dogs and in patients with hypertension.

STEFAN STANISLAUS FAJANS, M.D., Ann Arbor, Mich. A graduate of the University of Michigan (B.S., 1938; M.D., 1942), Dr. Fajans interned at the Mount Sinai Hospital, New York City, and served as medical officer in the U. S. Army. Returning to Ann Arbor in 1946, he has since held appointments in the University Hospital as research fellow, assistant resident, and resident, in internal medicine. Dr. Fajans' application was granted to enable him to undertake studies with Jerome W. Conn, M.D., F.A.C.P., in the Metabolism Research Unit and the Endocrinology and Metabolism Clinic of the University Hospital, to determine the physiological mechanisms capable of either stimulating or depressing the islets of Langerhans.

HORACE WILLIAM GERARDE, M.S., M.D., of Rockford, Ill. Dr. Gerarde, an exchange intern at the University of Iowa Hospitals, Iowa City, received his B.S. and M.S. in Chemistry degrees from Beloit College, and completed his medical course at the University of Wisconsin Medical School in 1948. He has held teaching assistantships in both institutions. During 1949–1950 Dr. Gerarde will study the histochemistry of certain liver diseases, under the direction of Drs. Mattill and Womack of the Departments of Biochemistry and Surgery, The State University of Iowa.

JOHN COLEMAN LAIDLAW, M.A., M.D., of Toronto, Canada. A former medical officer of the Royal Canadian Navy, Dr. Laidlaw attended the University of Toronto, where he obtained the B.A. degree in 1941, the

M.D. in 1944, and the M.A., in biochemistry, in 1947. He has served as interne in the Toronto General Hospital and as demonstrator in biochemistry in the University of Toronto. Now an assistant lecturer in biochemistry in the University College, London, England, Dr. Laidlaw proposes to continue studies there under Professor F. G. Young on the metabolism of certain cholinesterase inhibitors in regard to myasthenia gravis. Dr. Laidlaw has been designated by the Board of Regents as the ALFRED STENGEL RESEARCH FELLOW for 1949–1950.

JAMES METCALFE, JR., M.D., of Pigeon Cove, Mass. Presently a Lieutenant in the U. S. Naval Reserve, assigned to the Naval Hospital at Newport, R. I., Dr. Metcalfe is a graduate of Brown University (1943), and of the Harvard Medical School (1946). Before entering the Navy, he served as a medical house officer in the Peter Bent Brigham Hospital, Boston, 1946–1947. Dr. Metcalfe will devote his fellowship year to an investigation of the dynamics of circulation, with Dr. Eugene M. Landis, F.A.C.P., in the Department of Physiology, Harvard Medical School.

SAMUEL MOORE PEACOCK, JR., M.D., Philadelphia, Pa. Dr. Peacock is a Bachelor of Arts, Princeton University, 1944, and Doctor of Medicine, University of Pennsylvania School of Medicine, 1948. He is now an interne in the Bryn Mawr Hospital, Bryn Mawr, Pa. As a medical student, Dr. Peacock served as research assistant in the Eldridge R. Johnson Foundation for Medical Physics and the Department of Physical Medicine of the University of Pennsylvania. His fellowship will enable him to return to those departments to conduct cytochemical studies of nervous tissues during growth and other physiological activity, under the direction of Drs. Robert Hodes and Steven M. Horvath.

JACK LEONARD STROMINGER, M.D., Flushing, N. Y. An interne at the Barnes Hospital, St. Louis, Dr. Strominger received his A.B. degree from Harvard University in 1944, and his M.D. from the Yale University School of Medicine in 1948. It is his plan to devote his fellowship to studies of the microchemistry of brain tissue, with Professor O. H. Lowry in the Department of Pharmacology of the Washington University School of Medicine.

EDGAR WOODY, JR., M.D., Nashville, Tenn. Dr. Woody graduated from the University of Georgia in 1941 and took his M.D. degree from the Johns Hopkins University School of Medicine in 1944. Following an internship in the Union Memorial Hospital, Baltimore, Dr. Woody had military service from 1945 to 1947, and then was appointed to internships in pathology and in medicine in the Vanderbilt University Hospital. He will continue studies, now under way in the Departments of Medicine and Pathology of Vanderbilt University School of Medicine, on the combined effect of potassium iodide and streptomycin in tuberculosis.

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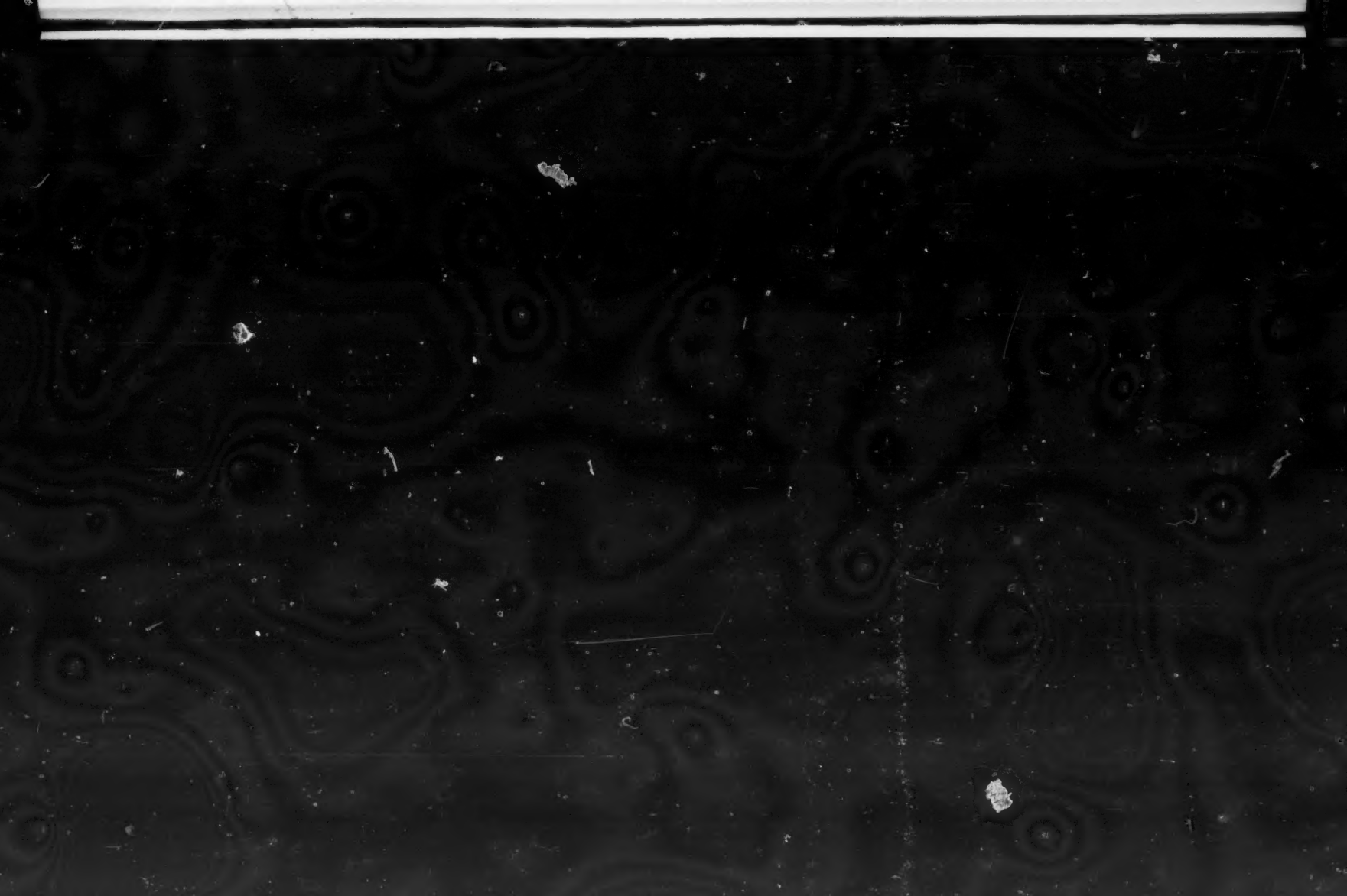

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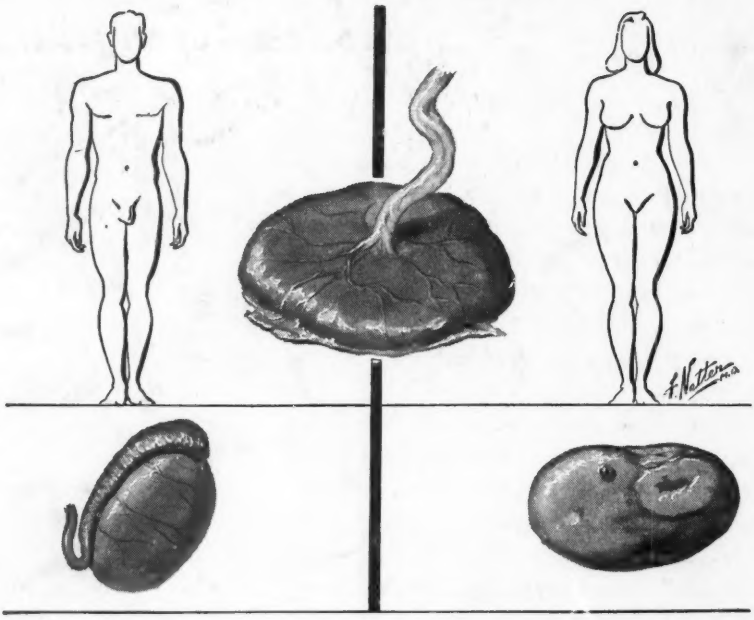

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